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Effects of Biologics on Fibrosis-4 Index in Patients with Psoriasis

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Background: Psoriasis is accompanied by systemic inflammation that includes the liver. The fibrosis-4 (FIB-4) index was developed to predict significant liver fibrosis. The present study evaluated the effects of biologics, including TNF inhibitors, on the FIB-4 index in psoriasis patients.

Methods: All adult patients with psoriasis who were prescribed biologics (TNF inhibitors, IL-17 inhibitors, or IL-23 inhibitors) at Nippon Medical School from June 2014 to January 2024 for the first time (biologic-naïve patients) were included in this study. The FIB-4 index was calculated before and after 6 months of treatment with biologics.

Results: A total of 105 patients were enrolled. The FIB-4 index was higher after 6 months of treatment with TNF inhibitors (P=0.0018) and IL-17 inhibitors (P=0.045) but did not change with IL-23 inhibitors. Aspartate aminotransferase and alanine aminotransferase levels did not change after treatment with TNF inhibitors, IL-17 inhibitors, or IL-23 inhibitors. Platelet count decreased after treatment with TNF inhibitors (P=0.0011) and IL-23 inhibitors (P=0.039) but did not change with IL-17 inhibitors.

Conclusions: Downregulation of platelets seems to be a major contributing factor for the increase in FIB-4 index in patients treated with TNF inhibitors. Although the FIB-4 index is a simple marker to screen for liver fibrosis, changes in this index should be interpreted with caution, and imaging findings such as transient elastography should also be used to evaluate the status of liver fibrosis.

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Key words: biologics, FIB-4 index, liver fibrosis, psoriasis, TNF inhibitor

Introduction

Psoriasis is a chronic, immune-mediated, hyperkeratotic skin disease[1,2] that is now understood to cause systemic inflammation which includes the liver. Metabolic dysfunction-associated steatotic liver disease (MASLD)[3], previously referred to as nonalcoholic fatty liver disease (NAFLD), is significantly correlated with psoriasis prevalence and severity[4–8]. Biologics have been available to treat refractory psoriasis since 2010 and, as of August 2024, 12 biologics can be used in Japan[9]. Three tumor necrosis factor (TNF) inhibitors (infliximab, adalimumab, and certolizumab pegol), four interleukin (IL)-17 inhibitors (secukinumab, ixekizumab, brodalumab, and bimekizumab), four IL-23 inhibitors (ustekinumab, guselkumab, risankizumab, and tildrakizumab), and one IL-36 inhibitor (spesolimab) are available.

The fibrosis-4 (FIB-4) index was developed as an index to predict liver fibrosis[10] and is used as a screening tool for psoriasis[11–13]. The FIB-4 index is classified as high (≥2.67), intermediate (1.30-2.66), and low (<1.30)[14]. Previously, we evaluated real-world screening data for liver fibrosis, including MASLD, using the FIB-4 index for psoriasis patients treated with biologics[15]. However, differences in the FIB-4 index before and after the use of bi-

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ologics were not examined.

Some studies have investigated the effects of biologics on the FIB-4 index in psoriasis patients[16–19]. Takamura et al.[16] reported that the FIB-4 index decreased after 6 months of treatment with IL-17 inhibitors (secukinumab and ixekizumab) in psoriasis patients. Takeshima et al.[17] showed that IL-23 inhibitors (guselkumab and risankizumab) decreased the FIB-4 index in psoriasis patients with an elevated FIB-4 index at 6 months after beginning treatment but that IL-17 inhibitors (secukinumab, ixekizumab, and brodalumab) did not. Matsuda et al.[18] reported that the FIB-4 index decreased after 6 months of treatment with brodalumab, which blocks both IL-17A and IL-17F, in psoriasis patients. Lebwohl et al.[19] found that the FIB-4 index did not increase through 2 years of treatment with bimekizumab, an IL-17A/F inhibitor. To our knowledge, no previous report examined the effect of TNF inhibitors on the FIB-4 index in psoriasis patients. Macia-Villa et al.[13] reported that liver fibrosis, as estimated by the FIB-4 index, was suppressed in patients with psoriatic arthritis who had been treated with biologics, 80.8% of whom had received TNF inhibitors. However, they did not compare the FIB-4 index before and after treatment. In this study, we evaluated the effects of multiple biologics, including TNF inhibitors, on the FIB-4 index in patients with psoriasis.

Methods

Data Collection

All patients with moderate to severe intractable psoriasis who were aged 20 years or older, prescribed biologics at Nippon Medical School from June 2014 to January 2024 for the first time (biologic-naïve patients), and observed for at least 6 months were included in this retrospective study. Intractable psoriasis was defined as psoriasis that did not adequately respond to topical treatment or standard systemic treatment, including phototherapy[9]. The psoriasis cases consisted of plaque-type psoriasis (psoriasis vulgaris: PsV), psoriatic arthritis (PsA), and generalized pustular psoriasis (GPP). The diagnostic criteria for the three types of psoriasis are described elsewhere[20]. The study was approved by the ethical committee of the Nippon Medical School (No. B-2021-415, F-2024-126). Patient consent was obtained by the opt-out method. Peripheral blood was obtained from each patient, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and the number of platelets (PLT) were measured before and after 6 months of treatment with biologics. The FIB-4 index was calculated as (age [yr] × AST [U/L])/(PLT [$\times 10^9$/L] × ALT [U/L]$^{1/2}$)[10]. Patients for whom an FIB-4 index could not be calculated because of missing data were excluded. One of eleven biologics—infliximab, adalimumab, certolizumab pegol, secukinumab, ixekizumab, brodalumab, bimekizumab, ustekinumab, guselkumab, risankizumab, or tildrakizumab—was administered to individual psoriasis patients in accordance with a protocol described elsewhere[9].

Statistical Analysis

Non-repeated measures ANOVA was used to compare ages and baseline FIB-4 indexes of patients treated with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors. If there was a significant difference, the Wilcoxon t-test with Bonferroni correction was used to perform multiple comparisons. When the number of patients exceeded 5, the Wilcoxon t-test was used to compare ALT levels, AST levels, PLT counts, and FIB-4 indexes before (baseline) and after treatment with biologics. Statistical analyses were performed using the Excel Statistical Program File ystat2008.xls[21]. A two-sided P-value of <0.05 was considered statistically significant.

Results

Patient Characteristics

In total, 105 patients (72 males) were included in this study. Median age was 53 years. Biologics prescribed for the first time and patient characteristics are shown in **Table 1**. TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors were initiated for 43 (41.0%), 30 (28.6%), and 32 (30.5%) patients, respectively. The median ages of the patients treated with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors were 51, 67.5, and 58.5 years, respectively. There were significant differences in age among patients treated with the three biologics (P=0.027). Patients treated with TNF inhibitors were younger than those treated with IL-17 inhibitors (P=0.000011) and IL-23 inhibitors (P=0.0033). There was no significant difference in age between patients treated with IL-17 inhibitors and IL-23 inhibitors. The numbers of patients with PsV, PsA, and GPP were 74 (70.5%), 25 (23.8%), and 6 (5.7%), respectively. The numbers of patients with PsA treated with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors were 24 (96.0%), 1 (4.0%), and 0 (0.0%), respectively. The numbers of patients with GPP treated with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors were 2 (33.3%), 2 (33.3%), and 2 (33.3%), respectively.

The overall median FIB-4 index before treatment (baseline) was 1.03 (**Table 1**). The median FIB-4 index values

Table 1 Initially prescribed biologics and patient characteristics

Biologics	n (%)	Median age	Sex (M:F)	PsA, n (%)	GPP, n (%)	Median FIB-4 index
All	105 (100.0)	53	72:33	25 (100.0)	6 (100.0)	1.03
TNFi	43 (41.0)	51	28:15	24 (96.0)	2 (33.3)	0.97
IFX	10 (9.5)	52	8:2	3 (12.0)	2 (33.3)	0.81
ADA	25 (23.8)	47	16:9	14 (56.0)	0 (0.0)	0.98
CER	8 (7.6)	52.5	4:4	7 (28.0)	0 (0.0)	1.20
IL-17i	30 (28.6)	67.5	23:7	1 (4.0)	2 (33.3)	1.40
SEC	16 (15.2)	67.5	14:2	1 (4.0)	2 (33.3)	1.20
IXE	5 (4.8)	51	3:2	0 (0.0)	0 (0.0)	1.06
BRO	8 (7.6)	72	5:3	0 (0.0)	0 (0.0)	2.06
BIM	1 (1.0)	58	1:0	0 (0.0)	0 (0.0)	1.00
IL-23i	32 (30.5)	58.5	21:11	0 (0.0)	2 (33.3)	1.19
UST	12 (11.4)	54	5:7	0 (0.0)	0 (0.0)	0.87
GUS	3 (2.9)	69	2:1	0 (0.0)	1 (16.7)	1.14
RIS	13 (12.4)	51	11:2	0 (0.0)	1 (16.7)	1.52
TIL	4 (3.8)	70	3:1	0 (0.0)	0 (0.0)	1.47

TNF, tumor necrosis factor; IL, interleukin; TNFi, TNF inhibitors; IL-17i, IL-17 inhibitors; IL-23i, IL-23 inhibitors; IFX, infliximab; ADA, adalimumab; CER, certolizumab pegol; SEC, secukinumab; IXE, ixekizumab; BRO, brodalumab; BIM, bimekizumab; UST, ustekinumab; GUS, guselkumab; RIS, risankizumab; TIL, tildrakizumab; PsA, psoriatic arthritis; GPP, generalized pustular psoriasis.

before treatment with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors were 0.97, 1.40, and 1.19, respectively. There were significant differences in baseline FIB-4 index values among patients treated with the three biologics (P=0.0055). The baseline FIB-4 index was lower for patients treated with TNF inhibitors than for those treated with IL-17 inhibitors (P=0.000025) and IL-23 inhibitors (P=0.0019). There was no significant difference in the baseline FIB-4 index between patients treated with IL-17 inhibitors and IL-23 inhibitors.

Changes in FIB-4 Index after Treatment with Biologics

Changes in FIB-4 index after treatment with biologics are shown in **Figure 1**. Overall, the FIB-4 index increased after treatment with biologics (P=0.00037). Specifically, the FIB-4 index increased after treatment with TNF inhibitors (P=0.0018) and IL-17 inhibitors (P=0.045) but did not change with IL-23 inhibitors. The FIB-4 index increased after treatment with adalimumab (P=0.013) and brodalumab (P=0.035) but did not change with infliximab, certolizumab pegol, secukinumab, brodalumab, ustekinumab, or risankizumab.

In patients aged <65 years (n=64), the FIB-4 index did not change after treatment with biologics (**Fig. 2**). The FIB-4 index increased after treatment with TNF inhibitors (P=0.025) but did not change with IL-17 inhibitors or IL-23 inhibitors. In patients aged ≥65 years (n=41), the FIB-4 index increased after treatment with biologics (P=0.0021). The FIB-4 index increased after treatment with TNF inhibitors (P=0.037) and IL-17 inhibitors (P=0.044) but did not change with IL-23 inhibitors.

In patients with a baseline FIB-4 index of <1.3 (n=64), the FIB-4 index increased after treatment with biologics (P=0.0016, **Fig. 3**). The FIB-4 index increased after treatment with TNF inhibitors (P=0.015) but did not change with IL-17 inhibitors or IL-23 inhibitors. In patients with a baseline FIB-4 index of ≥1.3 (n=41), the FIB-4 index did not change after treatment with biologics. The FIB-4 index did not change after treatment with TNF inhibitors, IL-17 inhibitors, or IL-23 inhibitors.

Changes in AST and ALT Levels and PLT Count after Treatment with Biologics

Neither AST nor ALT level changed after treatment with biologics. These levels did not change after treatment with TNF inhibitors, IL-17 inhibitors, or IL-23 inhibitors. Changes in $AST/ALT^{1/2}$ after treatment with biologics are shown in **Figure 4**. $AST/ALT^{1/2}$ did not change after treatment with biologics. These ratios did not change after treatment with TNF inhibitors, IL-17 inhibitors, or IL-23 inhibitor.

Changes in PLT count after treatment with biologics are shown in **Figure 5**. Overall, the PLT count decreased after treatment with biologics (P=0.000098). PLT count decreased after treatment with TNF inhibitors (P=0.0011) and IL-23 inhibitors (P=0.039) but did not change with IL-17 inhibitors.

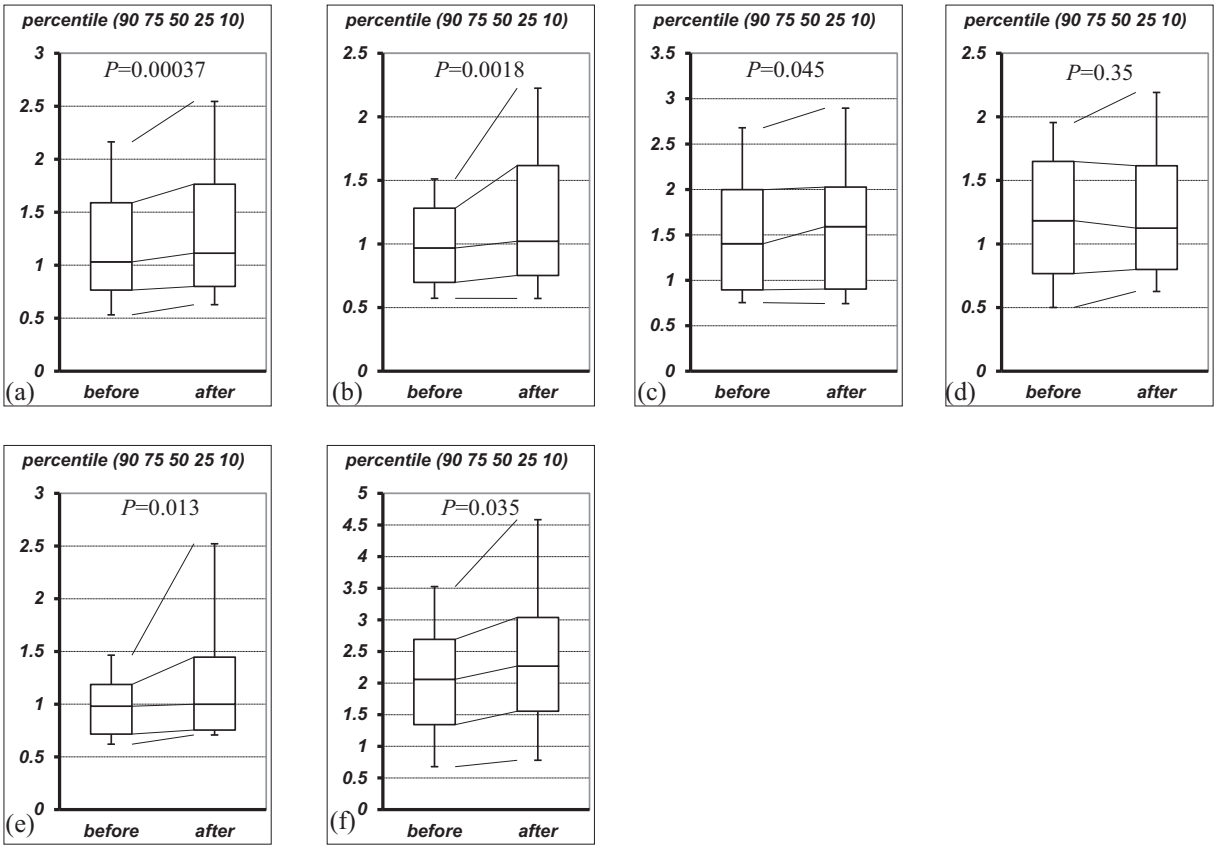

Fig. 1 Change in FIB-4 index after treatment with biologics. (a) All biologics. (b) TNF inhibitors. (c) IL-17 inhibitors. (d) IL-23 inhibitors. (e) Adalimumab. (f) Brodalumab.

Discussion

This is the first study to evaluate the effects of various biologics, including TNF inhibitors, on the FIB-4 index in psoriasis patients. In this study, patients using TNF inhibitors were significantly younger than patients using IL-17 and IL-23 inhibitors, as TNF inhibitors are less frequently used in elderly patients because of the difficulty of use, as compared with IL-17 and IL-23 inhibitors, in patients with a history of tuberculosis[9,15]. In addition, the baseline FIB-4 index was significantly lower for patients treated with TNF inhibitors than for patients treated with IL-17 inhibitors and IL-23 inhibitors. These results are unsurprising because age is included in the FIB-4 calculation formula and the FIB-4 index tends to be higher in elderly individuals[22].

Studies have evaluated the effects of biologics on the FIB-4 index in psoriasis patients. Takamura et al.[16] investigated the effects of the IL-17 inhibitors secukinumab and ixekizumab on hepatic fibrosis and its contributing factors. They enrolled 65 consecutive patients with psoriasis, and metabolic dysfunction-associated fatty liver disease (MAFLD) was observed in 82.6% of the enrolled patients. The numbers of patients treated with secukinumab and ixekizumab were 42 and 23, respectively. With regard to history of biologic treatment, the numbers of biologic-naïve and -switching patients were 14 and 51, respectively. The percentage of patients with a baseline FIB-4 index of ≥1.3 was 23.1%. Both the NAFLD fibrosis score and FIB-4 index significantly decreased after 6 months of treatment with IL-17 inhibitors, which indicates that upregulation of PLT count and downregulation of AST level were major contributing factors in the improvement of NAFLD fibrosis score.

Takeshima et al.[17] investigated the effects of IL-17 inhibitors and IL-23 inhibitors on FIB-4 index in psoriasis patients. A total of 171 consecutive psoriasis patients aged 36-64 years were included in the study. The numbers of biologic-naïve and -switching patients were 91 and 80, respectively. Thirty-four, 43, 21, 32, and 41 psoriasis patients were treated with secukinumab, ixekizumab, brodalumab, guselkumab, or risankizumab, respectively. With regard to the effects of biologics on the FIB-4 index, no significant change was observed in psoriasis patients treated with IL-17 inhibitors, IL-23 inhibitors, or any individual biologic. However, in psoriasis patients with a baseline FIB-4 index of >1.3, patients treated with

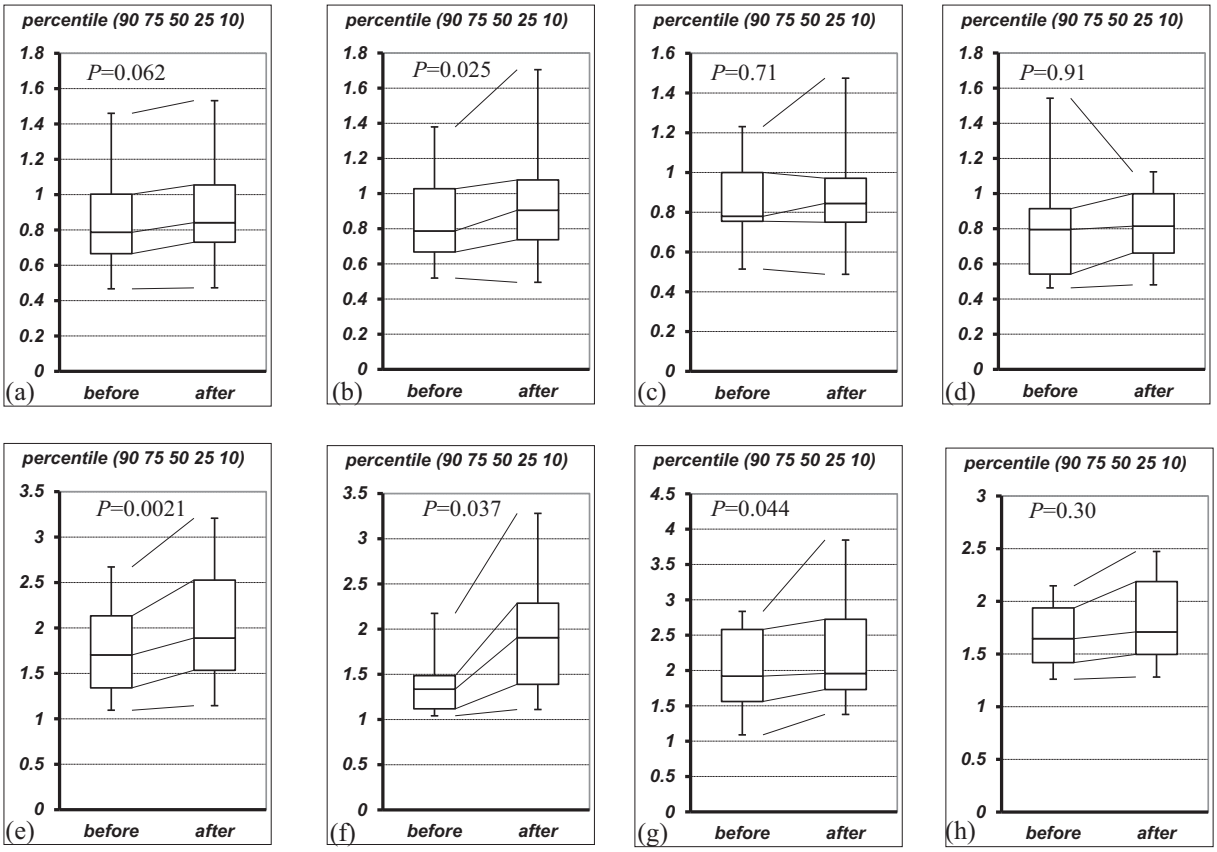

Fig. 2 Change in FIB-4 index after treatment with biologics in patients aged <65 years (a-d) and ≥65 years (e-h). (a, e) All biologics. (b, f) TNF inhibitors. (c, g) IL-17 inhibitors. (d, h) IL-23 inhibitors.

IL-23 inhibitors (and guselkumab individually), but not with IL-17 inhibitors, showed significantly decreased FIB-4 index scores after 6 months of treatment with biologics.

Matsuda et al.[18] evaluated longitudinal change in the FIB-4 index among psoriasis patients treated with brodalumab, which blocks IL-17 receptor A, inhibiting signal transduction mediated by IL-17A and IL-17F. They collected all psoriasis patients who first arrived at their clinic from April 2019 to March 2020. Of these, patients who were treated with brodalumab or secukinumab (an anti-IL-17A antibody) for more than 6 months were recruited. Those who were treated only with topical agents were selected as biologic-naïve controls. In the brodalumab group (n=5), the FIB-4 index was significantly lower, as compared to biologic-naïve controls (n=8) and the secukinumab group (n=7), at 6 months after the treatment.

Lebwohl et al.[19] investigated changes in FIB-4 index in patients treated with bimekizumab, an anti-IL-17A/F antibody, over 2 years in randomized phase 3/3b trials. A total of 2,186 patients was enrolled, and the FIB-4 index did not increase during the 2 years, regardless of the fibrosis risk at baseline. In patients with an FIB-4 index of ≥1.3 at baseline, the mean FIB-4 index scores (95% confidence interval) at baseline, 48 months, and 96 months after the treatment began were 1.71 (1.65, 1.78), 1.69 (1.59, 1.78), and 1.55 (1.44, 1.66), respectively. In the patients with an FIB-4 index of <1.3 at baseline, the mean FIB-4 index scores at baseline, and after 48 months, and 96 months of treatment, were 0.71 (0.70, 0.80), 0.76 (0.76, 0.80), and 0.76 (0.73, 0.78), respectively.

Macia-Villa et al.[13] evaluated the association between liver fibrosis and the HLA-Cw6 allele in PsA patients. A total of 209 PsA patients were enrolled: 25.3% were HLA-Cw6 positive, and among the 59.8% who had used biologics, 80.8% had used TNF inhibitors. The FIB-4 index was calculated to estimate liver fibrosis for 154/209 (73.7%) patients at onset, with a mean index of 1.53 ± 9.05; 58.9% were within the normal range (<1.3). At the latest available visit, the FIB-4 index could be calculated for 180/209 (86.1%) patients, with a mean index of 1.35 ± 0.85, of whom 86.4% were within the normal range. The HLA-Cw6 allele was more frequent in PsA patients with a normal current FIB-4 index than in those with an altered current FIB-4 index (18.54% vs. 6.74%). Biologics were more frequently used in PsA patients with a normal

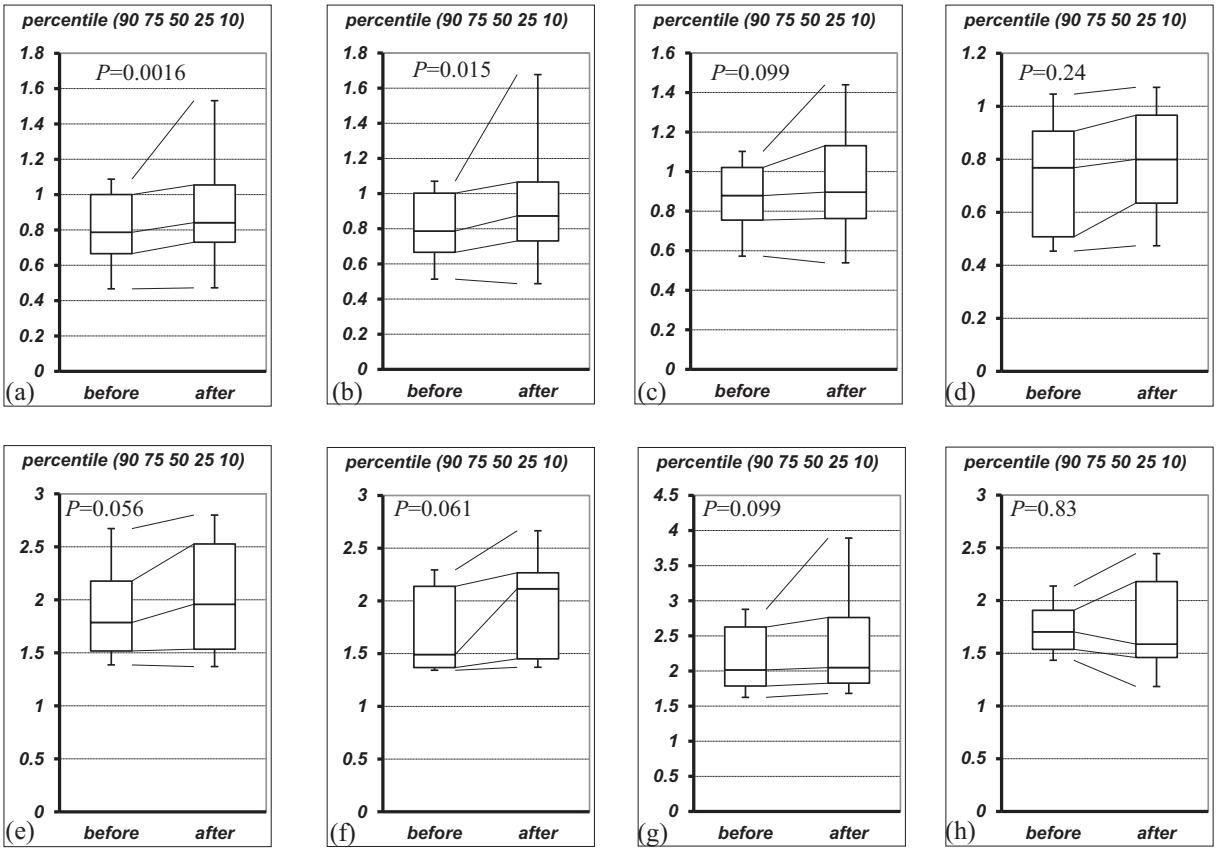

Fig. 3 Change in FIB-4 index after treatment with biologics in patients with a baseline FIB-4 index of <1.3 (a-d) and ≥1.3 (e-h). (a, e) All biologics. (b, f) TNF inhibitors. (c, g) IL-17 inhibitors. (d, h) IL-23 inhibitors.

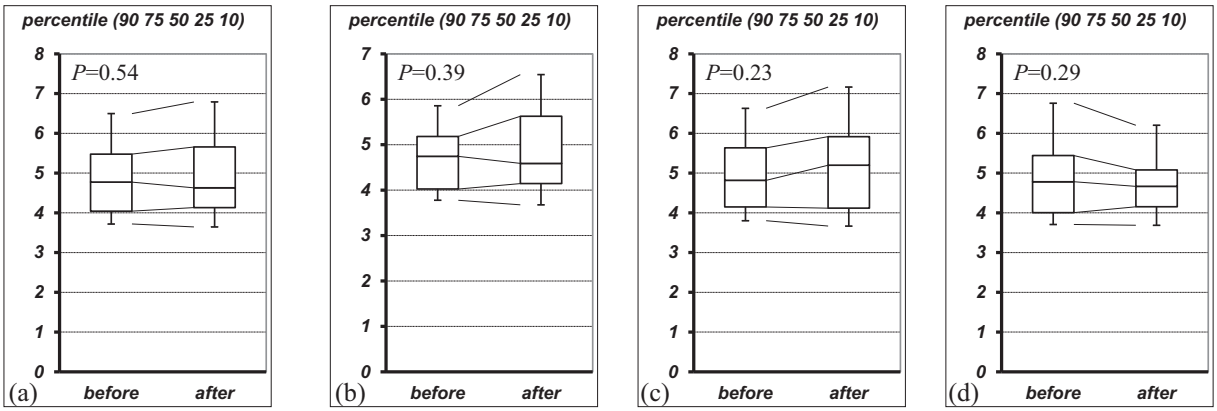

Fig. 4 Change in AST/ALT$^{1/2}$ after treatment with biologics. (a) All biologics. (b) TNF inhibitors. (c) IL-17 inhibitors. (d) IL-23 inhibitors.

current FIB-4 index than in those with an altered current FIB-4 index (64.3% vs. 35.7%). Thus, the researchers concluded that HLA-Cw6 and biologic therapy were protective factors against liver fibrosis in PsA patients. However, they did not directly compare FIB-4 index values before and after treatment with biologics.

In this study, we evaluated the effects of biologics, including TNF inhibitors, on the FIB-4 index in psoriasis patients. The FIB-4 index increased after treatment with biologics, TNF inhibitors, IL-17 inhibitors, adalimumab, and brodalumab but did not change with IL-23 inhibitors. In patients aged <65 years or with a baseline FIB-4 index of ≥1.3, the FIB-4 index did not change after treatment with biologics. In patients aged <65 and ≥65 years, the FIB-4 index increased after treatment with TNF inhibitors. The PLT count decreased after treatment with

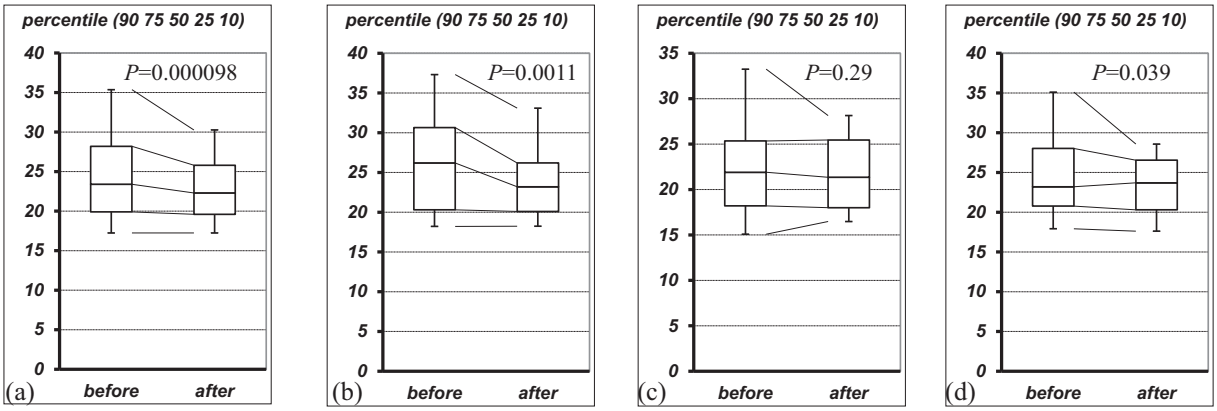

Fig. 5 Change in PLT count after treatment with biologics. (a) All biologics. (b) TNF inhibitors. (c) IL-17 inhibitors. (d) IL-23 inhibitors.

TNF inhibitors. Thus, downregulation of PLT count seems to be a major contributing factor in the increase in the FIB-4 index in patients treated with TNF inhibitors. Maya et al.[23] investigated change in PLT counts in 65 psoriatic patients treated with biologics. They compared PLT counts before and after 6 months of treatment with biologics. PLT count decreased by 17.4% during adalimumab therapy, 18.5% during infliximab therapy, 14.8% during ustekinumab therapy, and 18.5% during secukinumab therapy. They concluded that, although there may be an unknown common inhibitive mechanism of these biologics on megakaryocytes, the decrease in PLT count reflects remission of clinical manifestations achieved by biologics. It is true that the FIB-4 index is a simple and useful marker to screen the status of liver fibrosis, but caution is necessary when interpreting changes in the index. It is also necessary to perform image tests such as transient elastography to evaluate the status of liver fibrosis.

In our study, the FIB-4 index increased after treatment with TNF inhibitors and IL-17 inhibitors but did not change with IL-23 inhibitors. However, PLT count decreased after treatment with TNF inhibitors and IL-23 inhibitors but did not change with IL-17 inhibitors. Neither the AST nor ALT level changed after treatment with biologics. To evaluate changes in these markers in detail, we analyzed AST/ALT[1/2]. Although it tended to increase after treatment with IL-17 inhibitors and decrease with IL-23 inhibitors (**Fig. 4**), no significant difference was observed. Taken together, the main contributing factor to influence change in FIB-4 index seems to be PLT count, especially in the treatment with TNF inhibitors.

There are discrepancies between the results of our study and those of the four above-mentioned studies[16–19]. These discrepancies are mainly attributable to differences in the study subjects. We enrolled only patients who were prescribed biologics for the first time (biologic-naïve patients) to exclude the effects of previously used biologics (biologic-switching patients). In contrast, the studies by Takamura et al.[16] and Takeshima et al.[17] contained both biologic-naïve and -switching patients. Takamura et al.[16] reported that the FIB-4 index decreased after treatment with IL-17 inhibitors (secukinumab and ixekizumab), whereas, in our study, the FIB-4 index slightly increased after treatment with IL-17 inhibitors (secukinumab, ixekizumab, brodalumab, and bimekizumab). The index tended to decrease after treatment with ixekizumab (n=5: from 1.28 to 0.23, from 1.06 to 0.97, from 0.88 to 0.78, from 1.72 to 1.65, from 1.95 to 1.92) in our study. However, we could not analyze the data with the Wilcoxon t-test because n was <6. Matsuda et al.[18] showed that the FIB-4 index was lower after treatment with brodalumab (n=5), as compared with biologic-naïve controls (n=8). In contrast, in our study, the FIB-4 index slightly increased with treatment with brodalumab. This discrepancy may be due to the small number of patients. Takeshima et al.[17] reported that, in psoriatic patients aged 36-64 years with a baseline FIB-4 index of >1.3, the index decreased after treatment with IL-23 inhibitors. In our study, in patients aged <65 years or patients whose baseline FIB-4 index was ≥1.3, the FIB-4 index did not change after treatment with IL-23 inhibitors. With regard to patients aged 36–64 years with a baseline FIB-4 index of >1.3, the index tended to decrease after treatment with IL-23 inhibitors (n=3: from 1.50 to 1.17, from 1.63 to 1.49, from 1.71 to 1.11) in our study. However, we could not analyze data with the Wilcoxon t-test because n was <6. Thus, further study with a larger number of patients is necessary.

There are several limitations in this study. The number of patients examined was small. MASLD and alcoholic liver disease were analyzed together. The FIB-4 index was evaluated only at baseline and after 6 months of treatment with biologics. Image tests such as transient elastography were not performed to evaluate the status of liver fibrosis. The study was performed in a retrospective fashion. Therefore, prospective studies that have a larger number of patients, focus on MASLD for longer periods, and include findings from imaging are necessary.

In summary, we evaluated the effects of various biologics, including TNF inhibitors, on the FIB-4 index in 105 patients with psoriasis. The index increased after 6 months of treatment with TNF inhibitors and IL-17 inhibitors. PLT count decreased after treatment with TNF inhibitors and IL-23 inhibitors. Downregulation of PLT seems to be a major contributing factor in the increase in FIB-4 index in patients treated with TNF inhibitors. Although the FIB-4 index is a simple marker to screen the status of liver fibrosis, caution is necessary when interpreting changes in this index. It is also necessary to perform imaging studies such as transient elastography to evaluate the status of liver fibrosis.

Conflict of Interest: None declared.

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