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Association of Transition of Laboratory Markers with Transition of Disease Activity in Psoriasis Patients Treated with Biologics

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Background: Three categories of biologics―tumor necrosis factor (TNF) inhibitors, interleukin (IL)-17 inhibitors, and IL-23 inhibitors―are available for treatment of refractory psoriasis. Recent studies have shown that laboratory biomarkers such as peripheral blood neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), and serum C-reactive protein (CRP) levels are associated with psoriasis or its severity. This study evaluated associations of transition of NLR, PLR, MLR, and CRP with transition of disease activity in psoriasis patients treated with the three categories of biologics.

Methods: Data from 67 patients were analyzed. Associations of transition of psoriasis area and severity index (PASI) score with the abovementioned laboratory markers were evaluated by using a mixed effects model with PASI as the response variable, laboratory markers as fixed effects collectively, and patients as random effects.

Results: In an analysis of all the patients, serum CRP and NLR were associated with PASI score (P=0.006 and P=0.001, respectively). In patients treated with TNF inhibitors, CRP and NLR were associated with PASI score (P=0.043 and P=0.002, respectively). In patients treated with IL-17 inhibitors, NLR was associated with PASI score (P=0.001).

Conclusions: NLR appears to be the most reliable biomarker of the effect of treatment with biologics, especially IL-17 inhibitors. (J Nippon Med Sch 2022; 89: 587−593)

Key words: association study, biologics, disease activity, laboratory marker, transition

Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disease characterized by hyperproliferation of epidermal keratinocytes[1,2]. Recent studies have shown that novel laboratory biomarkers, such as peripheral blood neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and monocyte-lymphocyte ratio (MLR), along with serum C-reactive protein (CRP) level, are associated with psoriasis or its severity[3-14]. Biologics have been available for treatment of refractory psoriasis since 2010; as of March 2022, ten biologics were available in Japan[15]. They comprise three tumor necrosis factor (TNF) inhibitors (infliximab, adalimumab, and certolizumab pegol), three interleukin (IL)-17 inhibitors (secukinumab, ixekizumab, and brodalumab) and four IL-23 inhibitors (ustekinumab, guselkumab, risankizumab, and tildrakizumab). Time-course changes of the abovementioned biomarkers in patients after treatment with biologics (infliximab, adalimumab and ustekinumab) have been reported[8,13]; however, to our knowledge, no association study has evaluated the transition of these laboratory biomarkers and transition of disease activity in psoriasis patients treated with various biologics. This study evaluated the association of transition of NLR, PLR, MLR, and

CRP with transition of disease activity in patients after psoriasis treatment with the three categories of biologics.

Methods

Data Collection

This retrospective study analyzed the records of all patients aged 20 years or older with moderate to severe psoriasis who were prescribed biologics for the first time (bio-naïve patients) at Nippon Medical School during the period from June 2014 through April 2021 and observed for at least 3 months and 3 visits. The patients had plaque-type psoriasis (psoriasis vulgaris: PsV) or psoriatic arthritis (PsA). PsV was diagnosed after identifying the typical clinical features of scaly erythematous plaques, and PsA was diagnosed according to the classification criteria for psoriatic arthritis[16]. The study was approved by the ethical committee of the Nippon Medical School (Approval Number: B-2021-415). As a rule, patients visited our department at time 0, at 1 month after the start of biologics, and at least once every 3 months thereafter. Peripheral blood was obtained from all patients at each visit, and NLR, PLR, MLR, and serum CRP level were calculated. We recorded CRP values lower than 0.02 mg/dL as 0.02 mg/dL in this analysis, for descriptive purposes. The psoriasis area and severity index (PASI) score was evaluated as disease activity at every visit[17]. Patients without PASI scores from periodic evaluations were excluded from this study. Consent was obtained from all patients by using the opt-out method.

One of nine biologics—infliximab, adalimumab, certolizumab pegol, secukinumab, ixekizumab, brodalumab, ustekinumab, guselkumab, or risankizumab—was administered to each psoriasis patient according to a protocol described elsewhere[15]. The drug protocols were as follows: infliximab, 5 mg/kg at weeks 0, 2, and 6, and at 8-week intervals thereafter; adalimumab, initial dose of 80 mg followed by 40 mg at 2-week intervals; certolizumab pegol, 400 mg at 2-week intervals; secukinumab, 300 mg at weeks 0, 1, 2, 3, and 4, and at 4-week intervals thereafter; ixekizumab, initial dose 160 mg followed by 80 mg at 2-week intervals from weeks 2 to 12, and 80 mg at 4-week intervals thereafter; brodalumab, 210 mg at weeks 0, 1, and 2, and at 2-week intervals thereafter; guselkumab, 100 mg at weeks 0 and 4, and at 8-week intervals thereafter; and risankizumab, 150 mg at weeks 0 and 4, and at 12-week intervals thereafter. Patients were excluded if they showed any symptoms of infection at the time of blood examination, including cellulitis and pneumonia[8,13].

Statistical Analysis

Associations of transition in PASI score with transition in laboratory markers such as NLR, PLR, MLR, and CRP were evaluated by using a mixed effects model with PASI as the response variable, laboratory markers as fixed effects, and patients as random effects. The decision to perform logarithmic transformation for each laboratory marker in transition analysis was made after evaluating model fit with the Akaike information criterion (AIC). Model fit is better when the AIC is smaller[18]. Furthermore, regression coefficients of PASI and laboratory markers were calculated by using time series data from each patient in a simple linear regression model. Correlation coefficients between the regression coefficient of PASI and that of each laboratory marker were estimated. A P-value of less than 0.05 was considered to be significant, and all reported P-values were 2-sided. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC, USA).

Results

Descriptive Statistics

In total, 67 patients (51 men; 56 with PsV) were included in the analysis. Their characteristics in relation to type of biologic are shown in **Table 1**. Eleven of the 67 patients had PsA, and 10 of these PsA patients were treated with TNF inhibitors. Median PASI scores in the TNF, IL-17, and IL-23 inhibitor-treated groups were 11.2, 8.35, and 11.4, respectively, median CRP levels (mg/dL) were 0.21, 0.12, and 0.11, respectively, median NLR values were 2.56, 2.7, and 3.25, respectively, median PLR values were 128.22, 129.21, and 180.25, respectively, and median MLR were 0.21, 0.24, and 0.25, respectively. Transition diagrams of PASI score, serum CRP level, and NLR, PLR, and MLR are shown as box plots and line charts for individual patients in **Figure 1** and Supplementary **Figures 1～3** (https://doi.org/10.1292/jnms.JNMS.2022_89-613).

Analysis of Transition of PASI Score and Laboratory Markers

Because PASI scores were not normally distributed, we performed logarithmic transformation. In contrast, model fits (AIC) of the laboratory markers did not improve after logarithmic transformation (data not shown), so we did not use logarithmic transformation for any laboratory marker in transition analysis.

Table 2 shows the results of the mixed effects model with log (PASI) as the response variable, each laboratory marker as a fixed effect, separately or collectively, and

Table 1 Patient characteristics

Variable		Drug type		
		TNF inhibitors (n=20)	IL-17 inhibitors (n=26)	IL-23 inhibitors (n=21)
Age (years), median (range)		45 (27-72)	67 (33-80)	51 (26-90)
Male, no. (%)		15 (75.0)	20 (76.9)	15 (71.4)
Disease type, no. (%)	PsA	10 (50.0)	1 (3.9)	0 (0)
	PsV	10 (50.0)	25 (96.1)	21 (100)
Drug, no. (%)	ADA	17 (85.0)	BRO 6 (23.1)	GUS 4 (19.0)
	CER	1 (5.0)	IXE 6 (23.1)	RIS 9 (42.9)
	IFX	2 (10.0)	SEC 14 (53.8)	UST 8 (38.1)
PASI, median (range)		11.2 (4.8-21.8)	8.35 (4.8-35.4)	11.4 (5.4-31.9)
WBC, median (range)		7.2 (4.2-8.8)	6.45 (4.2-10.3)	7 (3.9-10.6)
Neu (%), median (range)		65.95 (55-75.4)	64.75 (34.3-82)	67.5 (51.8-84.4)
Lym (%), median (range)		25.9 (11-36.7)	23.85 (11.8-57.4)	20.3 (10.4-39.4)
Mon (%), median (range)		5.45 (3.8-10.4)	5.5 (1.4-7.6)	4.9 (2.3-12.1)
PLT (×10³/μL), median (range)		253.5 (174-378)	210.5 (113-435)	224 (116-360)
CRP (mg/dL), median (range)		0.21 (0.02-7.99)	0.12 (0.02-2.71)	0.11 (0.03-3.34)
NLR, median (range)		2.56 (1.5-6.85)	2.7 (0.6-6.95)	3.25 (1.31-7.92)
PLR, median (range)		128.22 (93.89-346.39)	129.21 (79.88-315.12)	180.25 (44.61-348.36)
MLR, median (range)		0.21 (0.13-0.95)	0.24 (0.07-0.48)	0.25 (0.12-0.62)

PsA, psoriatic arthritis; PsV, psoriasis vulgaris; ADA, adalimumab; CER, certolizumab pegol; IFX, infliximab; BRO, brodalumab; IXE, ixekizumab; SEC, secukinumab; GUS, guselkumab; RIS, risankizumab; UST, ustekinumab; PASI, psoriasis area and severity index; Neu, neutrophil; Lym, lymphocyte; Mon, monocyte; PLT, platelet; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio

patients as random effects. We chose to focus on the results of "a fixed effect collectively." An analysis of all patients showed that serum CRP and NLR were associated with PASI score (P=0.005 and P=0.001, respectively). In patients treated with TNF inhibitors and IL-17 inhibitors, NLR was associated with PASI score (P=0.002 and P=0.001, respectively). In patients treated with IL-23 inhibitors, PLR was associated with PASI score (P=0.039).

The correlation coefficients between the regression coefficient of log (PASI) and those of the laboratory markers are shown in **Table 3**. With regard to serum CRP, we performed logarithmic transformation to make the time series data linear. Among all patients, the correlation coefficients for NLR and MLR were 0.46 (P<0.001) and 0.54 (P<0.001), respectively. Among patients treated with IL-17 inhibitors, the correlation coefficients for NLR and MLR were 0.55 (P=0.004) and 0.61 (P=0.001), respectively. Among patients treated with IL-23 inhibitors, the correlation coefficient for MLR was 0.66 (P=0.001).

Discussion

Serum TARC/CCL17 level is closely related to atopic dermatitis (AD) disease activity[19], and its measurement is reimbursed by health insurance in Japan. However, such a specific and easily accessible laboratory biomarker has not been established for psoriasis. Recent studies found that the laboratory biomarkers NLR, PLR, MLR, and CRP were associated with psoriasis or its severity, although these biomarkers are also indicators of systemic inflammation in variety of diseases, including cancer, cardiovascular disease, and autoimmune inflammatory disease[20,21]. We previously reported that transitions of serum TARC levels and eosinophil numbers were strongly associated with that of AD activity and that transitions of serum lactate dehydrogenase (LDH) and immunoglobulin E (IgE) levels were weakly associated and not associated, respectively, with that of AD activity, in 2006[22]. Furthermore, we found that in AD patients treated with dupilumab, a monoclonal antibody against IL-4 receptor α, which has been available since 2018, transitions of serum TARC and LDH were associated strongly with that of AD activity, but that transitions of serum IgE level and eosinophil count were moderately associated and weakly associated with AD activity, respectively[18]. These two studies indicate that the utility of a laboratory marker depends on the drugs used for treatment. The present study evaluated the association of transition of NLR, PLR, MLR, and CRP with transition of disease activity in psoriasis patients after treatment with different categories of biologics and attempted to identify the most reliable laboratory marker among the four abovementioned markers.

(a) PASI

(b) PASI

(c) CRP

(d) CRP

(e) NLR

(f) NLR

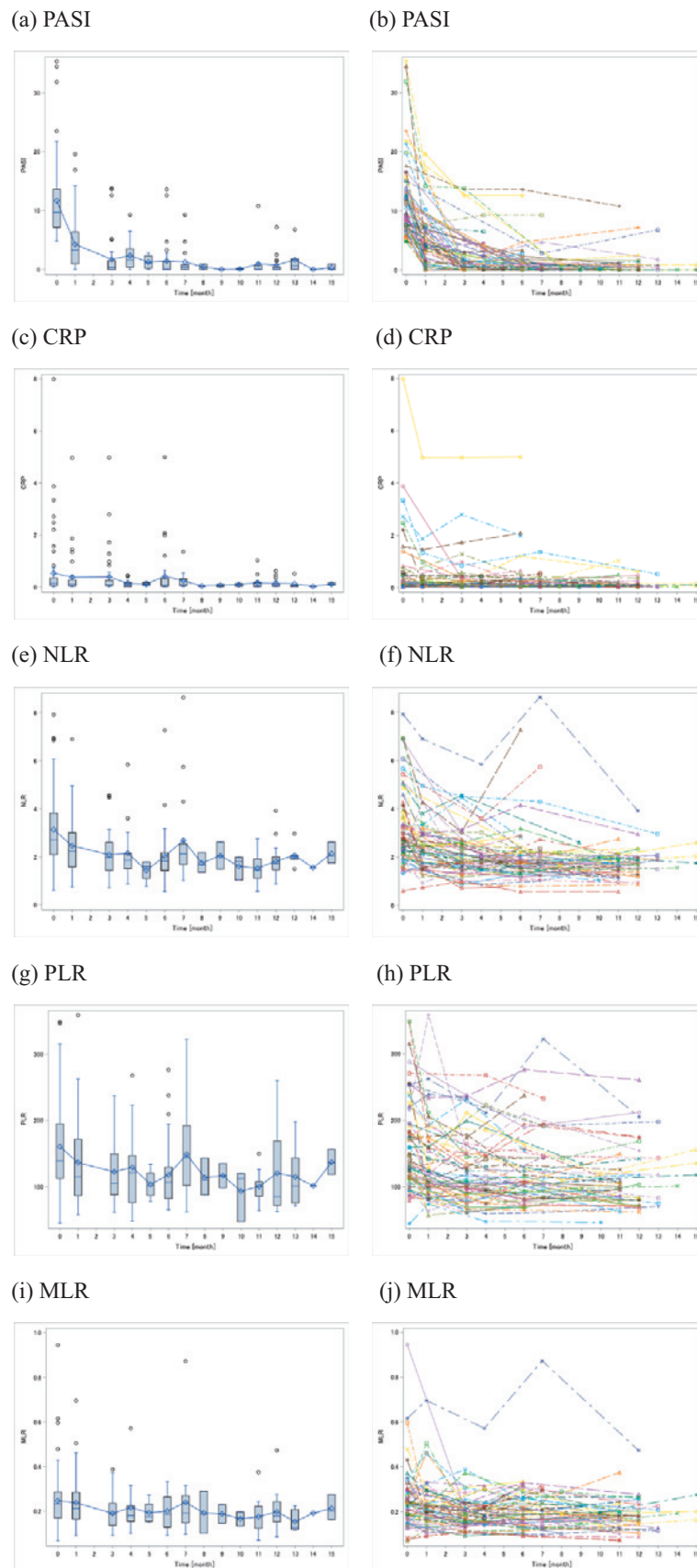(g) PLR

(h) PLR

(i) MLR

(j) MLR

Fig. 1 Transition diagrams of PASI score (a, b), serum CRP level (c, d), and NLR (e, f), PLR (g, h), and MLR (i, j) for all patients are shown as box plots (a, c, e, g, i) and line charts of individual patients (b, d, f, h, j).

Table 2 Results of mixed model with log (PASI) as response variable, each laboratory marker as a fixed effect, and patients as random effects

	Fixed effect separately				Fixed effect collectively			
	Estimate	SE	t-value	P-value	Estimate	SE	t-value	P-value
All patients (n=67)								
CRP	0.35	0.07	4.93	<0.001	0.22	0.08	2.82	0.005
NLR	0.36	0.05	7.40	<0.001	0.30	0.08	3.51	0.001
PLR	0.01	0.001	5.98	<0.001	0.002	0.002	1.05	0.297
MLR	2.43	0.59	4.110	<0.001	−0.78	0.81	−0.97	0.333
Patients treated with TNF inhibitors (n=20)								
CRP	0.31	0.08	3.94	<0.001	0.16	0.09	1.84	0.071
NLR	0.66	0.11	6.05	<0.001	0.73	0.22	3.26	0.002
PLR	0.01	0.00	4.96	<0.001	0.002	0.003	0.60	0.551
MLR	3.90	1.07	3.63	<0.001	−2.25	1.68	−1.34	0.185
Patients treated with IL-17 inhibitors (n=26)								
CRP	0.32	0.18	1.79	0.077	−0.004	0.19	−0.02	0.983
NLR	0.32	0.08	4.17	<0.001	0.46	0.13	3.47	0.001
PLR	0.003	0.002	1.88	0.064	−0.003	0.002	−1.37	0.173
MLR	2.43	1.13	2.16	0.034	−0.70	1.42	−0.49	0.624
Patients treated with IL-23 inhibitors (n=21)								
CRP	0.60	0.20	2.95	0.004	0.37	0.21	1.77	0.082
NLR	0.26	0.07	3.79	<0.001	0.13	0.13	1.00	0.320
PLR	0.01	0.002	4.09	<0.001	0.01	0.002	2.11	0.039
MLR	1.23	0.82	1.50	0.138	−1.39	1.14	−1.22	0.228

SE: standard error

Table 3 Correlation coefficients between regression coefficient of log (PASI) and those of the laboratory markers

	Association with regression coefficient of log (PASI)*	P-value
All patients		
Log (CRP)	0.19	0.118
NLR	0.46	<0.001
PLR	0.11	0.390
MLR	0.54	<0.001
Patients treated with TNF inhibitors		
Log (CRP)	0.07	0.777
NLR	0.34	0.149
PLR	0.06	0.816
MLR	0.29	0.216
Patients treated with IL-17 inhibitors		
Log (CRP)	0.38	0.053
NLR	0.55	0.004
PLR	0.01	0.960
MLR	0.61	0.001
Patients treated with IL-23 inhibitors		
Log (CRP)	0.11	0.642
NLR	0.39	0.081
PLR	0.27	0.243
MLR	0.66	0.001

*Pearson product–moment correlation coefficient

CRP is an acute-phase serum protein that is one of the most sensitive markers of inflammation, including PsA[8].

In this study, 11 of the 67 patients had PsA, and 10 of the PsA patients were treated with TNF inhibitors. CRP level

was higher for patients treated with TNF inhibitors (median: 0.21 mg/dL) than for those treated with IL-17 inhibitors (median: 0.12) or IL-23 inhibitors (0.11). In the analysis of all patients, CRP as a fixed effect was associated with log (PASI) as the response variable (P<0.005, **Table 2**), but the correlation coefficient between the regression coefficient of log (PASI) and log (CRP) was 0.19 (P=0.118, **Table 3**). In addition, the correlation coefficient between the regression coefficient of log (PASI) and log (CRP) in patients treated with TNF inhibitors was 0.07 (P =0.777, **Table 3**). There are a number of potential explanations for the lack of association between transition of CRP and transition of PASI score. First, the number of enrolled patients was small. Second, we used the conventional method for CRP quantification, not the high-sensitivity CRP method that can detect CRP values lower than 0.02 mg/dL. Third, PASI score and arthritis activity did not always correspond in PsA patients. Future studies should analyze the association of CRP with transition of arthritis activity, using the Disease Activity Score-28 for rheumatoid arthritis[23].

NLR, PLR, and MLR are indicators of systemic inflammation, and recent studies showed that these markers were also associated with psoriasis or its severity. NLR was reported to be elevated in psoriasis patients[9–12,14], and some reports noted a positive correlation between PASI and NLR[9,12–14]. Yurtdaş et al. reported that PLR was higher in psoriasis patients[10], and some studies noted a positive correlation between PASI and PLR[12–14]. Aktaş Karabay et al. found higher MLR values in patients with psoriasis and a positive correlation between PASI and MLR[14]. Furthermore, Asahina et al. showed that NLR and PLR decreased after treatment with the biologics infliximab, adalimumab, and ustekinumab[13]; however, there has been no association study of the transition of these biomarkers and transition of disease activity in psoriasis patients treated with various biologics.

It is difficult to identify the most reliable biomarker from the present data. However, the results shown in **Tables 2, 3**, especially those for the mixed effects model with log (PASI) as the response variable, each laboratory marker as a fixed effect collectively, and patients as random effects, which is the most fundamental analysis in this study, suggest that NLR is the most reliable biomarker of the treatment effect of biologics, especially IL-17 inhibitors. There are a number of possible reasons for the strong association in time-course change between NLR and PASI in patients treated with IL-17 inhibitor. First, the number of patients treated was higher for IL-17 inhibitors (n=26) than for TNF inhibitors (n=20) or IL-23 inhibitors (n=21). Second, because IL-17 inhibitors block the most downstream portion of the psoriatic inflammatory cascade, they have a rapid effect. NLR and PLR are reported to decrease quickly in psoriasis patients treated with biologics[13], which explains the strong association in IL-17 inhibitor-treated patients.

This study has limitations. The number of patients examined was small, serum CRP was measured by a conventional method, itch intensity was not checked, and comorbidities were not considered. In addition, the analysis was performed retrospectively. Thus, prospective studies with a larger number of patients are necessary.

In summary, our results suggest that NLR is one of the most reliable biomarkers of the effect of treatment with biologics, especially IL-17 inhibitors. NLR is simple and easily calculated in daily clinical practice and can provide early detection of systemic inflammation, such as cardiovascular comorbidities, in patients with psoriasis.

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