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Change in Serum KL-6 Level during Biologic Treatment for Psoriasis

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Background: We previously analyzed data from blood examination screenings, including serum Krebs von den Lungen (KL)-6 level, before starting biologic treatment for psoriasis in a real-world setting. However, we did not follow change in KL-6 level after the initiation of biologics. Furthermore, there has been no follow-up study of certolizumab pegol, risankizumab, or tildrakizumab. This study evaluated change in serum KL-6 levels in patients during treatment with biologics, including certolizumab pegol, risankizumab, and tildrakizumab.

Methods: We analyzed data from 111 patients. Change in KL-6 level was regarded as significant if it increased to greater than 500 U/mL at least once and if the maximum level after treatment with biologics was at least 1.5 times that of the baseline level.

Results: KL-6 level significantly changed during treatment with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors in 9 (20.9%), 2 (6.3%), and 2 (5.6%) patients, respectively. Mean age, mean baseline KL-6 level, and frequency of TNF inhibitor use were higher in patients with a significant change in KL-6 level than those in patients without a significant change. Ten patients had minor interstitial changes on chest CT scans but no clinical signs suggesting interstitial pneumonia.

Conclusions: Older patients with psoriasis and high baseline KL-6 levels must be carefully monitored during treatment with biologics, especially TNF inhibitors. Monitoring of KL-6 level and chest CT scans is necessary to exclude the possibility of drug-induced interstitial pneumonia.

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Key words: Krebs von den Lungen-6 (KL-6), biologics, changes, psoriasis, tumor necrosis factor inhibitor

Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disease characterized by hyperproliferation of epidermal keratinocytes[1,2]. In Japan biologics have been available for treatment of refractory psoriasis since 2010, and 11 biologics were available as of September 2022[3]. They consist of 3 tumor necrosis factor (TNF) inhibitors (infliximab, adalimumab, and certolizumab pegol), 4 interleukin (IL)-17 inhibitors (secukinumab, ixekizumab, brodalumab, and bimekizumab), and 4 IL-23 inhibitors (ustekinumab, guselkumab, risankizumab, and tildrakizumab).

The Biologics Review Committee of the Japanese Dermatological Association for Psoriasis recommends blood testing to determine Krebs von den Lungen (KL)-6 levels before and after initiation of biologics at screening and monitoring[3]. In post-marketing surveillance of infliximab, adalimumab, and ustekinumab, interstitial pneumonia (IP) was occasionally reported[3]. Previously, we evaluated blood examination screening data, including serum KL-6 levels, before initiation of biologics, for 127 psoriasis patients in a real-world setting[4]. Seven (5.5%) patients had KL-6 levels higher than the reference value (500 U/mL)[4]. However, we did not follow change in KL-6 level after initiation of biologics.

Several studies have reported elevated serum KL-6 lev-

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els during treatment with TNF inhibitors in psoriasis patients with and without IP[5–8]. In contrast, ustekinumab did not increase serum KL-6 level[5,6]. Furthermore, IL-17 inhibitors, including secukinumab, decreased elevated or high baseline KL-6 levels in patients with psoriasis[9–11]. A recent follow-up study of biologics—including TNF inhibitors (infliximab and adalimumab), IL-17 inhibitors (secukinumab, ixekizumab, and brodalumab), and IL-23 inhibitors (ustekinumab and guselkumab)—found that neither IL-17 inhibitors nor IL-23 inhibitors significantly affected serum KL-6 level[12]. The authors also detailed changes in KL-6 levels over time during biologic therapy in individual patients[12]. However, there has been no such study of certolizumab pegol, risankizumab, or tildrakizumab. This study therefore evaluated change in serum KL-6 level in individual patients treated with biologics, including certolizumab pegol, risankizumab, and tildrakizumab.

Methods

Data Collection

This retrospective study analyzed data from all patients with intractable psoriasis aged 15 years and older who received a first prescription for biologics (bio-naïve patients) at Nippon Medical School from June 2014 through November 2021 and were observed for at least 6 months[13]. The psoriasis diagnoses comprised plaque-type psoriasis (psoriasis vulgaris: PsV), psoriatic arthritis (PsA), and generalized pustular psoriasis (GPP). The 3 types of psoriasis were diagnosed as described elsewhere[4]. No patient had adenocarcinoma, including colon, breast, or pancreatic cancer. The patients visited our department at time 0, at 1 month after initiation of biologics, and at least once every 3 months thereafter[13].

Peripheral blood was obtained from each patient at each visit (in most cases) and KL-6 levels were measured[13] with a specific enzyme-linked immunosorbent kit (Sekisui Medical, Tokyo, Japan) by our in-house laboratory; 500 U/mL was considered the upper limit of the normal range. The study was approved by the ethics committee of the Nippon Medical School (No. 2022-217). Consent was obtained by the opt-out method in all patients. One of the following 10 biologics—infliximab, adalimumab, certolizumab pegol, secukinumab, ixekizumab, brodalumab, ustekinumab, guselkumab, risankizumab, or tildrakizumab—was administered to the patients, in accordance with a protocol described elsewhere[4].

Statistical Analysis

Change in KL-6 was regarded as significant when KL-6 level increased to greater than 500 U/mL and the maximum level after treatment with biologics was at least 1.5 times that of the baseline level[14,15]. The paired *t* test was used to compare baseline KL-6 level and maximum KL-6 level after treatment. Non-repeated measures ANOVA was used to compare rate of change in maximum KL-6 level after treatment with the baseline level among patients treated with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors, and among patients treated with infliximab, adalimumab, and certolizumab pegol. The Fisher exact test was used to compare sex (female), baseline KL-6 level, and the biologic used between patients with and without a significant change in KL-6 level during treatment with biologics. The unpaired *t* test was used to compare the mean ages of patients with and without a significant change in KL-6 levels during treatment with biologics. Statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical School)[16]. A two-sided *P*-value of <0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 111 patients (77 males) were included in this study[13]. Mean (±SD) patient age was 56.7 ± 16.8 years. The numbers of patients with PsV, PsA, and GPP were 81 (73.0%), 24 (21.6%), and 6 (5.4%), respectively[13]. The initial biologic prescribed, patient characteristics, and duration of use are shown in **Table 1**. TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors were initiated for 43 (38.7%), 32 (28.8%), and 36 (32.4%) patients, respectively[13]. The mean ages of patients treated with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors were 52.5, 61.8, and 57.3 years, respectively. The numbers of patients with PsA treated with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors were 23 (53.4%), 1 (3.1%), and 0 (0.0%), respectively. The numbers of patients with GPP treated with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors were 2 (4.7%), 3 (9.4%), and 1 (2.8%), respectively.

The mean KL-6 level was 255.1 ± 137.3 (U/mL). The number of patients with a KL-6 level higher than the reference value (500 U/mL) was 7 (6.3%), among whom the values were 588.1, 613.7, 621.9, 624.4, 684.7, 753.2, and 791.2 U/mL[4]. Neither chest CT performed before initiation of biologics nor clinical signs indicated a diagnosis of IP in any patient[4].

Table 1 Initially prescribed biologics, patient characteristics, and duration of use

Biologics	n (%)	Age*	Sex (M:F)	PsA, n (%)	GPP, n (%)	Durations of use#
TNFi	43 (38.7)	52.5 ± 14.2	29:14	23 (53.4)	2 (4.7)	37.2 ± 27.8
IFX	10 (9.0)	53.1 ± 10.5	8:2	3 (30.0)	2 (20.0)	48.6 ± 33.5
ADA	28 (25.2)	51.3 ± 15.7	19:9	16 (57.1)	0 (0.0)	37.4 ± 16.0
CER	5 (4.5)	58.2 ± 11.7	2:3	4 (80.0)	0 (0.0)	13.4 ± 1.5
IL-17i	32 (28.8)	61.8 ± 16.5	24:8	1 (3.1)	3 (9.4)	34.7 ± 25.1
SEC	17 (15.3)	62.4 ± 14.5	15:2	1 (5.9)	2 (11.8)	40.9 ± 29.1
IXE	6 (5.4)	53.3 ± 12.1	4:2	0 (0.0)	0 (0.0)	43.4 ± 7.4
BRO	9 (8.1)	62.9 ± 21.8	5:4	0 (0.0)	1 (11.1)	17.1 ± 15.4
IL-23i	36 (32.4)	57.3 ± 18.9	24:12	0 (0.0)	1 (2.8)	25.5 ± 19.1
UST	17 (15.3)	51.5 ± 19.2	9:8	0 (0.0)	0 (0.0)	29.8 ± 24.1
GUS	4 (3.6)	68.3 ± 12.8	2:2	0 (0.0)	1 (25.0)	36.5 ± 9.0
RIS	10 (9.0)	59.2 ± 18.8	9:1	0 (0.0)	0 (0.0)	23.1 ± 8.5
TIL	5 (4.5)	64.8 ± 19.4	4:1	0 (0.0)	0 (0.0)	6.8 ± 0.4

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; UST, ustekinumab; GUS, guselkumab; RIS, risankizumab; TIL, tildrakizumab; *mean ± standard deviation (years); PsA, psoriatic arthritis; GPP, generalized pustular psoriasis; #mean ± standard deviation (months)

Table 2 Change in KL-6 level during treatment with biologics

Biologics	n	Mean KL-6 (U/mL)		Mean rates of change (SD)	*P* value	≥1.5#, n (%)	Significant change$, n (%)
		Baseline (SD)	After* (SD)				
TNFi	43	274.4 (164.1)	455.1 (344.8)	1.80 (1.45)	0.0006	19 (44.2)	9 (20.9)
IFX	10	196.9 (82.8)	476.0 (305.8)	2.94 (2.65)	0.03	7 (70.0)	2 (20.0)
ADA	28	304.6 (189.9)	465.6 (385.9)	1.47 (0.55)	0.003	10 (35.7)	6 (21.4)
CER	5	260.1 (49.9)	354.6 (138.9)	1.32 (0.28)	0.08	2 (40.0)	1 (20.0)
IL-17i	32	242.4 (138.8)	298.9 (179.7)	1.26 (0.30)	0.002	6 (18.8)	2 (6.3)
SEC	17	255.0 (125.7)	346.6 (214.3)	1.34 (0.26)	0.002	5 (29.4)	2 (11.7)
IXE	6	160.6 (32.2)	210.6 (59.6)	1.34 (0.43)	0.11	1 (16.7)	0 (0.0)
BRO	9	273.2 (189.6)	267.4 (138.6)	1.06 (0.19)	0.78	0 (0.0)	0 (0.0)
IL-23i	36	243.3 (95.8)	300.4 (171.6)	1.23 (0.42)	0.009	8 (22.2)	2 (5.6)
UST	17	241.1 (104.0)	280.0 (123.4)	1.17 (0.21)	0.002	3 (17.6)	0 (0.0)
GUS	4	203.1 (87.5)	416.7 (363.2)	1.88 (0.93)	0.25	3 (75.0)	1 (25.0)
RIS	10	273.4 (92.3)	315.9 (179.1)	1.12 (0.29)	0.28	1 (10.0)	1 (10.0)
TIL	5	223.2 (87.6)	245.6 (78.4)	1.14 (0.21)	0.13	1 (20.0)	0 (0.0)

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; UST, ustekinumab; GUS, guselkumab; RIS, risankizumab; TIL, tildrakizumab; SD, standard deviation; *the maximum KL-6 levels after treatment; #the maximum KL-6 levels after treatment were 1.5-fold or greater than the baseline levels; $KL-6 level at some point was more than 500 U/mL and maximum level after treatment were 1.5-fold or greater than the baseline levels.

Change in Serum KL-6 Level during Treatment with Biologics

Change in serum KL-6 level during treatment with biologics is shown in **Table 2**. The mean baseline KL-6 level, maximum level after treatment, and the mean rate of change in patients treated with TNF inhibitors (n=43) were 274.4 U/mL, 455.1 U/mL, and 1.80, respectively. The corresponding values were 242.4 U/mL, 298.9 U/mL, and 1.26 in patients treated with IL-17 inhibitors (n=32) and 243.3 U/mL, 300.4 U/mL, and 1.23 in patients treated with IL-23 inhibitors (n=36). There were significant differences in the mean rate of change among patients treated with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors (P=0.01). The mean KL-6 level at baseline, maximum KL-6 level after treatment, and mean rate of change were 196.9 U/mL, 476.0 U/mL, and 2.94, respectively, in patients treated with infliximab (n=10); 304.6 U/mL, 465.6 U/mL, and 1.47 in patients treated

Table 3 Baseline characteristics and biologics prescribed for patients with and without a significant change in KL-6 level during treatment with biologics

	Patients with a significant change (n = 13)	Patients without a significant change (n = 98)	P value
Sex (female) [a]	6 (46.2)	28 (28.6)	0.21
Age (years) [b]	72.4 ± 10.5	54.7 ± 16.4	2.51×10^{-4}**
Baseline KL-6 (U/mL) [b]	420.8 ± 185.2	233.1 ± 114.0	1.25×10^{-6}**
TNFi users[a]	9 (69.2)	34 (34.7)	0.0304*
IL-17i users[a]	2 (15.4)	30 (30.6)	0.3407
IL-23i users[a]	2 (15.4)	34 (34.7)	0.2161

TNF, tumor necrosis factor; IL, interleukin; TNFi, TNF inhibitors; IL-17i, IL-17 inhibitors; IL-23i, IL-23 inhibitors

[a] Data provided as n (%), analyzed by Fisher's exact test

[b] Data provided as the mean ± standard deviation, analyzed by unpaired t test

*Statistically significant at $P < 0.05$, ** at $P < 0.01$.

with adalimumab (n=28); and 260.1 U/mL, 354.6 U/mL, and 1.32 in patients treated with certolizumab pegol. There were significant differences in the mean rate of change among patients treated with infliximab, adalimumab, and certolizumab pegol (P=0.01). The numbers of patients with a significant change in KL-6 level (ie, a KL-6 level of >500 U/mL at least once, and a maximum KL-6 level after treatment that was 1.5 times that at baseline) treated with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors were 9 (20.9%), 2 (6.3%), and 2 (5.6%), respectively.

Table 3 shows the baseline characteristics and biologics used for patients with and without a significant change in KL-6 level during treatment with biologics. The difference in the proportion of women with and without a significant change—46.2% and 28.6%, respectively—was not significant (P=0.21). The ages of patients with a significant change were higher than those of patients without a significant change (72.4 ± 10.5 vs. 54.7 ± 10.5, $P = 2.51\times10^{-4}$). The baseline KL-6 levels of patients with a significant change were higher than those of patients without a significant change (420.8 ± 185.2 vs. 233.1 ± 114.0, $P = 1.25 \times 10^{-6}$). The proportion of TNF inhibitor users among patients with a significant change was higher than that in patients without a significant change (69.2% vs. 34.7%, P = 0.03). The proportion of IL-17 inhibitor users and IL-23 inhibitor users among patients with a significant change were not significantly different from those in patients without a significant change.

Figure 1 shows change in serum KL-6 level during treatment with biologics in patients with a KL-6 level greater than 500 U/mL at least once (Cases 1-18). Thirteen patients (Cases 1-3, 5-8, 10-13, 17, and 18) had a significant change in KL-6 level. Among these patients, infliximab, adalimumab, certolizumab pegol, secukinumab, guselkumab, and risankizumab were initiated in 2 (cases 1 and 2), 6 (cases 3, 5-8, and 10), 1 (case 11), 2 (cases 12 and 13), 1 (case 17), and 1 (case 18), respectively. In cases 5 and 7, adalimumab was replaced by brodalumab and ustekinumab, respectively. Methotrexate (MTX) 2 mg/week was concomitantly used for 2 months (from the 11 th to the 13th month after initiation of infliximab) in case 2 for reduction of arthralgia by PsA but was discontinued because of liver dysfunction. Only case 18 had a past history of IP. In 10 patients (cases 1, 3-5, 7, 10, 13, 15, 17, 18), minor interstitial changes were noted on a chest CT scan during treatment. The patients were examined by pulmonologists, but no clinical signs suggesting IP were found and they were carefully monitored while continuing treatment with biologics.

Discussion

We carefully evaluated change in KL-6 level during treatment with biologics, including certolizumab pegol, risankizumab, and tildrakizumab. In patients treated with infliximab (n=10), the mean rate of change rate in KL-6 was high (2.94) and 20.0% of patients had a significant change in KL-6 level, which is consistent with previous reports[6–8,12]. In patients treated with adalimumab (n=28), the mean rate of change of KL-6 was relatively high (1.47) and 21.4% of patients had a significant change in KL-6 level, which is also consistent with previous reports[5–8]. This is the first study of certolizumab pegol (n=5), and the mean rate of change of KL-6 was 1.32, which was almost the same as the rates for secukinumab (1.34) and ixekizumab (1.34), but 20.0% of patients had a sig-

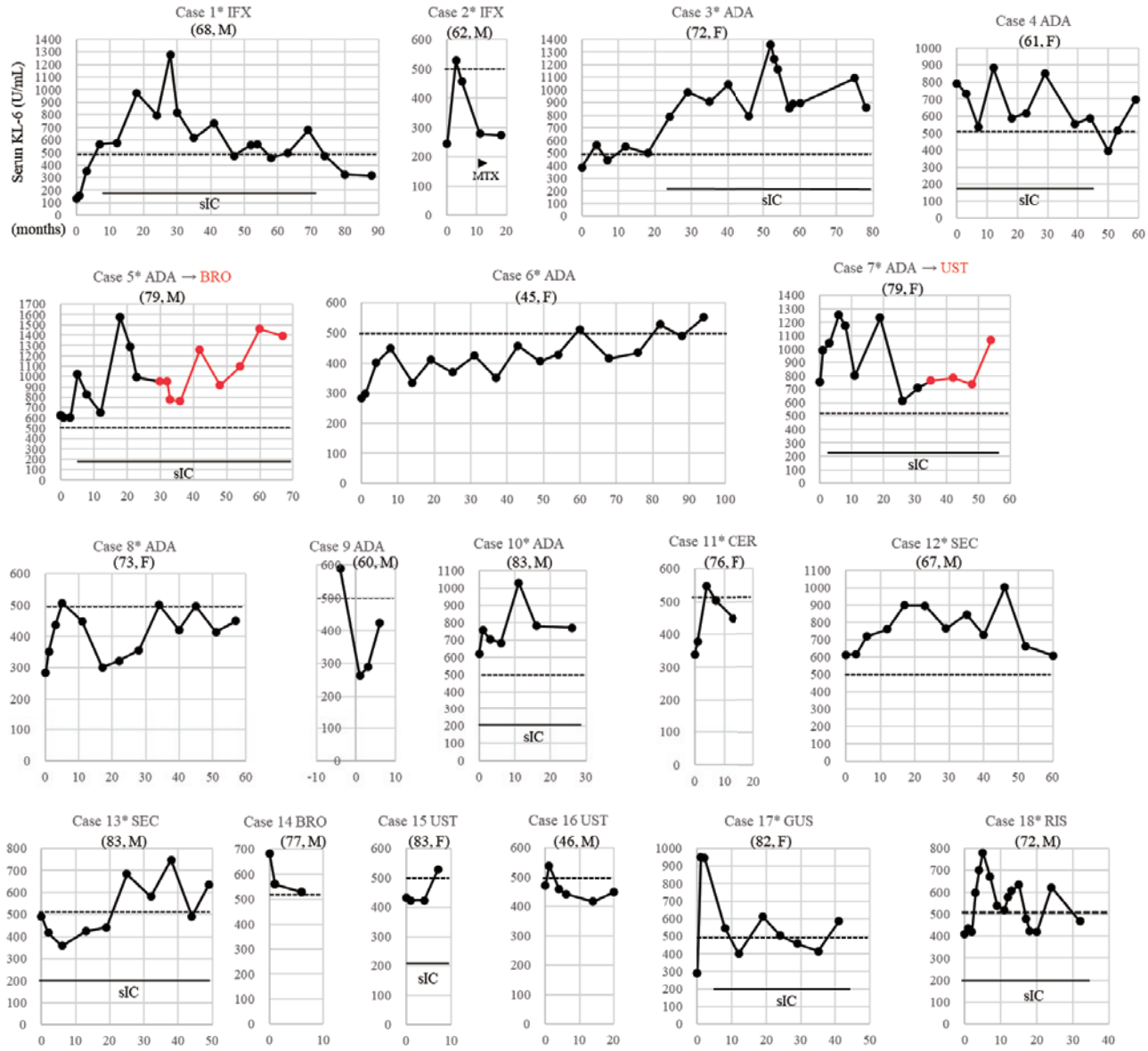

Fig. 1 Change in serum KL-6 levels during treatment with biologics in patients with a KL-6 level greater than 500 U/mL at least once.

*Patients with a significant change in KL-6 level (KL-6 level >500 U/mL at least once and a maximum level after treatment that was at least 1.5 times that of the baseline level: cases 1-3, 5-8, 10-13, 17, 18). In cases 5 and 7, adalimumab was replaced by brodalumab and ustekinumab, respectively (red line). Methotrexate (MTX) 2 mg/week was concomitantly used for 2 months (from the 11th to the 13th month after initiation of infliximab) in case 2.

IFX, infliximab; ADA, adalimumab; BRO, brodalumab; UST, ustekinumab; CER, certolizumab pegol; SEC, secukinumab; GUS, guselkumab; RIS, risankizumab; sIC, slight interstitial change on CT.

nificant change in KL-6 level. Harigai et al. reported elevation of serum KL-6 levels in clinical trials of TNF inhibitors in patients with rheumatoid arthritis (RA)[14]. In RISING, a clinical trial for infliximab, 15.6% of the enrolled patients showed a significant change in KL-6 level by week 54. In HIKARI, 7.8% of a certolizumab pegol group and 0% of a placebo group had significant changes in KL-6 levels by week 24[14]. A retrospective study of serum KL-6 levels during biologic treatment for RA[15] reported that 18.0%, 16.0%, and 27.3% of RA patients treated with infliximab, etanercept, and adalimumab, respectively, had a significant change in KL-6 levels by 12 months[15]. The results of these reports suggest that all TNF inhibitors, including certolizumab pegol, elevate serum KL-6 level, although the degree varies. The precise mechanism by which TNF inhibitors increase serum KL-6 levels without the apparent presence of IP is unclear[6]. TNF-α-converting enzyme (TACE), also known as a disintegrin and metalloproteinase 17 (ADAM17), the protease responsible for TNF-α shedding from its transmem-

brane[17], was shown to shed membrane-bound KL-6[17]. TNF inhibitors may increase TACE expression as a feedback mechanism that augments shedding of KL-6 into pulmonary epithelial fluid[8].

In patients treated with secukinumab (n=17), the mean rate of change in KL-6 was 1.34 and 11.7% of patients had a significant change in KL-6 level. In patients treated with ixekizumab (n=6), the mean rate of change in KL-6 was 1.34 but no patient had a significant change in KL-6 level. In patients treated with brodalumab (n=9), the mean rate of change of KL-6 was the lowest (1.16) and no patient had a significant change in KL-6 level. Chijiwa et al. reported that secukinumab decreased elevated serum KL-6 levels in patients with psoriasis[9]. Kurita et al. showed that treatment with TNF inhibitors increased serum KL-6 levels but that levels returned to baseline during 2 years of secukinumab treatment[10]. Hara et al. reported that although IL-17 inhibitors did not affect KL-6 levels in the overall study population, they decreased KL-6 levels in a group with high baseline KL-6, regardless of recognizable IP[11]. IL-17 was reported to be involved in inflammatory and fibrotic processes in the lung[19], suggesting that IL-17A has important roles in the development of IP[11]. Hara et al. also reported that treatment with the IL-17 inhibitors secukinumab, ixekizumab, and brodalumab tended to decrease the ratio of KL-6 at 3 months in the group with a high baseline KL-6[11]. While secukinumab and ixekizumab tended to decrease the ratio of KL-6 at 6 months, brodalumab significantly lowered it at 6 months[11]. Interestingly, we found that the mean rate of change in KL-6 was lowest (1.16) in patients treated with brodalumab. Thus, among the IL-17 inhibitors, brodalumab seems to have the strongest effect on KL-6 level.

In patients treated with ustekinumab (n=17), the mean rate of change in KL-6 was low (1.17) and no patient had a significant change in KL-6 level, which is consistent with previous reports[5,6,12]. In patients treated with guselkumab (n=4), the mean rate of change in KL-6 was high (1.88) and one patient had a significant change in KL-6 level, which is inconsistent with a previous report[12]. The most likely explanation for this discrepancy is the small sample size of our study (n=4). Among patients treated with risankizumab (n=10), the mean rate of change in KL-6 was low (1.12) but one patient had a significant change in KL-6 level. In patients treated with tildrakizumab (n=5), the mean rate of change in KL-6 was low (1.14) and no patient had a significant change in KL-6 level. To evaluate the effects of guselkumab, risankizumab, and tildrakizumab on KL-6 level, larger-scale studies will be necessary.

The ages and baseline KL-6 levels of patients with significant changes were higher than those of patients without a significant change. Miyagawa et al. reported the characteristics of IL-17/23 inhibitor-induced IP in patients with psoriasis[20]. Six patients treated with IL-17/23 inhibitors (ustekinumab: 3, guselkumab: 1, secukinumab: 2) of a total of 603 patients (ustekinumab: 256, guselkumab: 53, secukinumab: 183, ixekizumab: 183, brodalumab: 72) developed drug-induced IP. Older age and higher baseline KL-6 level were associated with development of drug-induced IP[20], which is consistent with our results, although no patient developed clinically apparent IP in our study. There are other reports of IP induced by IL-17/23 inhibitors, including ustekinumab, secukinumab, and ixekizumab[21–25]. However, to our knowledge, there has been no English report of a patient with psoriasis developing IP induced by brodalumab, which is consistent with our results. Ishibashi and Shiiyama reported a case of psoriasis vulgaris treated with brodalumab in a hemodialysis patient with end-stage renal disease due to diabetic nephropathy[26]. The patient developed chronic cough after initiation of brodalumab, and CT showed a diffuse ground-glass shadow and pleural effusion in both lungs. Transbronchial lung biopsy disclosed no finding suggestive of IP, so brodalumab was continued. The respiratory symptoms improved with proper weight setting and adequate dietary control[26]. The frequency of TNF inhibitor use in patients with significant change was higher than that in patients without a significant change. It is necessary to carefully monitor elderly patients with high baseline KL-6 levels while using biologics, especially TNF inhibitors.

In case 2 in **Figure 1**, MTX 2 mg/week was concomitantly used for 2 months with infliximab. Only one other patient received concomitant MTX (2 mg/week) and biologic (infliximab) treatment for 11 months[13], and in this patient the KL-6 level did not change significantly. Takamura et al. reported that 27 (17.9%) of 151 RA patients treated with biologics, including infliximab, etanercept, adalimumab, and tocilizumab (IL-6 inhibitor), and 5 (10.6%) of 47 patients treated without biologics but with MTX, showed a significant change in KL-6 level by 12 months[15]. Although we cannot completely exclude the possibility that MTX affected change in KL-6 levels in case 2, the low dose, short period of administration, and timing of concomitant MTX make it unlikely that MTX had an effect on change in KL-6 level in this patient.

Case 18 had a past history of IP, but there was no other patient with such a history in this study. Miyagawa et al. reported that pre-existing IP was associated with development of drug-induced IP[20]. Matsumoto et al. reported that 3 of 11 cases with drug-induced IP were associated with secukinumab, ustekinumab, and ixekizumab and that these 3 cases also had a history of drug-induced IP[25]. It is necessary to carefully monitor patients with a past history of IP when using biologics. In 10 patients (cases 1, 3-5, 7, 10, 13, 15, 17, 18), minor interstitial changes were seen on chest CT scans of patients without clinical signs suggesting IP, indicating that the these patients may have had subclinical IP. Furthermore, in 2 patients aged 83 years (cases 13 and 15) CT scans showed minor interstitial changes before KL-6 levels exceeded 500 U/mL. Thus, it is necessary to carefully monitor elderly patients by checking serum KL-6 level and chest CT scans to rule out development of drug-induced IP.

This study had limitations. The number of patients examined was small. The duration of use of biologics varied, and durations were short for newly approved drugs such as certolizumab pegol and tildrakizumab, which might have affected the results[13]. We did not evaluate comorbidities, including metabolic syndrome and smoking habits, which might have affected the results. In addition, this study was performed retrospectively. Therefore, prospective studies of a larger number of patients with the same duration of biologic use are necessary.

In summary, we evaluated change in KL-6 levels in 111 psoriasis patients during treatment with 10 biologics, including certolizumab pegol, risankizumab, and tildrakizumab. The numbers of patients with a significant change in KL-6 levels treated with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors were 9 (20.9%), 2 (6.3%), and 2 (5.6%), respectively. The ages and the baseline KL-6 levels of patients with significant changes were higher than those of patients without a significant change. Minor interstitial changes were evident on chest CT scans of 10 patients without clinical signs of IP. To rule out development of drug-induced IP, it is necessary to carefully monitor elderly patients with high baseline KL-6 levels during treatment with biologics, especially TNF inhibitors, by checking KL-6 level and chest CT scans, and consulting pulmonologists when necessary.

Conflict of Interest: None declared.

References

1. Kanda N, Hoashi T, Saeki H. Nutrition and psoriasis. Int J Mol Sci. 2020 Jul;21(5):5405.
2. Kanda N, Hoashi T, Saeki H. The defect in regulatory T cells in psoriasis and therapeutic approaches. J Clin Med. 2021 Aug;10(17):3880.
3. Saeki H, Terui T, Morita A, et al. Japanese guidance for use of biologics for psoriasis (the 2019 version). J Dermatol. 2020 Mar;47(3):201−22.
4. Ozaki S, Ichiyama S, Ito M, Hoashi T, Kanda N, Saeki H. Real-world blood examination screening data before initiation of biologics for psoriasis patients. J Dermatol. 2022;49(5):534−8.
5. Mabuchi T, Yamaoka H, Kawai M, Ota T, Ozawa A. Elevation of serum KL-6 levels during treatment with tumor necrosis factor-α inhibitor in patients with psoriasis. J Dermatol. 2014;41(12):1136−7.
6. Yanaba K, Umezawa Y, Sakakihara R, et al. Infliximab and adalimumab, unlike ustekinumab, increase serum KL-6 levels in Japanese patients with psoriasis. J Dermatol. 2015;42(8):828−9.
7. Higashi Y, Tada K, Shimokawa M, Kawai K, Kanekura T. Elevation of serum KL-6 in patients with psoriasis treated with anti-tumor necrosis factor-α therapy. Clin Exp Dermatol. 2016;41(1):88−90.
8. Hayashi M, Yanaba K, Umezawa Y, Asahina A, Nakagawa H. Impact of anti-tumor necrosis factor-a agents on serum levels of KL-6 and surfactant protein-D in patients with psoriasis. J Dermatol. 2016;44(9):1063−6.
9. Chijiwa C, Takeoka S, Kamata M, et al. Secukinumab decreases serum Kreb von den Lugen 6 (KL-6) level in patients with psoriasis with elevated serum KL-6 level. Br J Dermatol. 2018;179(6):1396−7.
10. Kurita M, Kikuchi S, Umezawa Y, Asahina A, Nakagawa H, Yanaba K. Serum KL-6 levels in Japanese patients with psoriasis treated with secukinumab. J Dermatol. 2019;46(4):e115−6.
11. Hara H, Miyagawa H, Araya J, et al. Effect of anti-interleukin-17 biologics on Kreb von den Lugen-6 level in patients with psoriasis. J Dermatol. 2021;48(6):886−93.
12. Iwata H, Haga N, Sugai T, Fujita Y. Serum Krebs von den Lugen-6 levels in psoriatic patients under treatment with biologics. J Dermatol. 2021;48(3):376−9.
13. Miyazaki S, Ozaki S, Ichiyama S, et al. Changes in antinuclear antibody titers over time during biologic treatment for psoriasis. J Nippon Med Sch. 2022;90:96−102.
14. Harigai M, Takamura A, Atsumi T, et al. Elevation of KL-6 levels in clinical trials of tumor necrosis factor inhibitors in patients with rheumatoid arthritis: a report from the Japan College of Rheumatology Ad Hoc Committee for Safety of Biological DMARDS. Mod Rheumatol. 2013;23(2):284−96.
15. Takamura A, Hirata S, Nagasawa H, et al. A retrospective study of serum KL-6 levels during treatment with biological disease-modifying antirheumatic drugs in rheumatoid arthritis patients: a report from the Ad Hoc Committee for safety of Biological DMARDs of the Japan College of Rheumatology. Mod Rheumatol. 2013;23(2):297−303.
16. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013 Mar;48(3):452−8.
17. Black RA, Rauch CT, Kozlosky CJ, et al. A metalloproteinase disintegrin that releases tumor-necrosis factor-α from cells. Nature. 1997;385(6618):729−33.
18. Ishikawa N, Hattori N, Yokoyama A, Kohno N. Utility of KL-6/MUC1 in the clinical management of interstitial lung disease. Respir Investig. 2012;50(1):3−13.
19. Mi S, Li Z, Yang HZ, et al. Blocking IL-17A promotes the

resolution of pulmonary inflammation and fibrosis via TGF-β-1 dependent and -independent mechanism. J Immunol. 2011;187(6):3003−14.
20. Miyagawa H, Hara H, Araya J, et al. Characteristics of anti-IL-17/23 biologics-induced interstitial pneumonia in patients with psoriasis. PLoS One. 2021;16(1):e0245284.
21. Kajihara I, Yamada-Kanazawa S, Maeda-Otsuka S, et al. Secukinumab-induced interstitial pneumonia in a patient with psoriasis vulgaris. J Dermatol. 2017;44(12):e322−3.
22. Hayashi M, Igarashi A, Okumura K, Suzuki T. Paradoxical exacerbation of latent pneumonia by secukinumab in a patient with psoriasis vulgaris. Br J Dermatol. 2019;180 (3):684−5.
23. Lee SG, An JH, Kim DH, Yoon MS, Lee HJ. A case of interstitial lung disease and autoimmune thyroiditis associated with ustekinumab. Acta Derm Venereol. 2019;99(3): 331−2.
24. Matsumoto Y, Abe N, Tobita R, et al. The risk of interstitial lung disease during biological treatment in Japanese patients with psoriasis. Clin Exp Dermatol. 2020;45(7): 853−8.
25. Oka R, Inoue T, Hashimoto A, Tsuruta N, Nagase K, Sugita K. Improvement of ixekizumab-related interstitial pneumonia following its discontinuation in a patient with psoriatic arthritis. Eur J Dermatol. 2020;32(2):281−2.
26. Ishibashi M, Shiiyama R. A case of psoriasis vulgaris treated with brodalmab in a hemodialysis patient with end-stage renal disease due to diabetic nephropathy. Case Rep Dermatol Med. 2020;3863152.

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