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1 Serum KL-6 levels in psoriasis patients under treatment with biologics

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5 Running head: KL-6 in psoriasis with biologics

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10

1 **Abstract**

2 During biological treatments, attention should be paid to adverse reactions, particularly to infectious  
3 diseases. Furthermore, drug-induced interstitial lung disease (ILD) is also known to be associated with  
4 biological therapies. We retrospectively reviewed serum KL-6 levels in psoriasis patients who  
5 underwent treatment with 7 different biologics. A total of 67 patients who received 80 biological  
6 treatments were evaluated. The 31 anti-TNF $\alpha$  treatments consisted of 17 infliximab (IFX) and 14  
7 adalimumab (ADA). The 23 anti-IL23 treatments consisted of 14 ustekinumab (UST) and 9  
8 guselkumab (GUS). The 26 anti-IL17 treatments consisted of 9 secukinumab (SEC), 6 ixekizumab  
9 (IXE), and 11 brodalumab (BRO). The IFX showed significantly increased mean serum KL-6  
10 (170.9%), but none of the other treatments showed significant increases. 13 of the 17 (75.6%) patients  
11 in the IFX and 17 of the 31 (54.8%) patients in the total anti-TNF $\alpha$  group demonstrated at least a 25%  
12 increase in serum KL-6. Levels exceeding the cutoff (500 U/ml) were detected in 3 patients before  
13 treatment and in 7 patients after treatment. This study showed that anti-IL17 and anti-IL23 treatments  
14 have no significant impact of serum KL-6 level. In addition to the influence of IFX, a significantly  
15 large number of patients in the IFX group have a history of MTX administration associated with  
16 psoriatic arthritis, which may influence the KL-6 level. None of the patients with elevated serum  
17 KL-6 showed pulmonary changes by CT scan and/or X-ray.

18

## 1 Introduction

2           Biologics are known to be highly effective against severe psoriasis vulgaris and psoriatic  
3 arthritis. Regarding the pathomechanisms of psoriasis, several cytokines, including tumor  
4 necrosis factor (TNF) $\alpha$ , interleukin (IL)-23, and IL-17, play critical roles, and biologics block  
5 these cytokines or their receptors. Several adverse reactions caused by biological therapies have  
6 been reported<sup>1,2</sup>. Under anti-TNF $\alpha$  therapies for psoriasis, interstitial lung disease (ILD) was  
7 reported as an adverse event<sup>3,4</sup>. Krebs von den Lungen-6 (KL-6), which is a human mucin-1  
8 (MUC1) protein, is a mucinous sialylated sugar chain on MUC1<sup>5</sup>. MUC1 is expressed by mucus  
9 epithelial cells in various organs, such as the lungs, stomach, and intestines. MUC1 consists of  
10 three domains: extracellular, transmembrane, and intracellular<sup>6</sup>. The extracellular domain of  
11 MUC1 is highly glycosylated, and one sialylated sugar chain is recognized by anti-KL-6 mAb<sup>5</sup>.  
12 Serum KL-6 levels are elevated not only with ILD, but also with several adenocarcinomas,  
13 including colon cancer, breast cancer and pancreas cancer<sup>6</sup>. In ILD, KL-6 is produced by type II  
14 pneumocytes<sup>7</sup>.

15           Several studies have investigated the influence of biologics on serum KL-6 levels<sup>8-11</sup>.  
16 We here retrospectively review KL-6 levels in psoriasis patients who received 7 different  
17 biological treatments.

18

## 1 **Methods**

2           This study was approved by the Hokkaido University Certified Review Board and was  
3 performed in accordance with the Declaration of Helsinki. We retrospectively reviewed patient  
4 information from 2010 January to 2019 December, including psoriasis patients treated with  
5 biologics. The study analyzed patients whose blood tests included KL-6 level at least twice during  
6 their observation period. We took blood samples and chest X-rays regularly according to the  
7 Japanese guidelines for biologic interventions for psoriasis<sup>12</sup>. Serum KL-6 levels were measured  
8 by chemiluminescent enzyme immunoassay (Sekisui Medical, Tokyo, Japan), and 500 U/ml was  
9 considered the upper limit for normal. None of the patients had active adenocarcinomas, which  
10 are known to elevate KL-6 levels.

11           To compare KL-6 levels before versus after biologics therapy, p-values were determined  
12 using the Student's t-test.

13

## 14 **Results**

15 Serum KL-6 levels were found to be significantly elevated after anti-TNF $\alpha$  treatment

16           A total of 67 patients and 80 biological treatments (median age: 57 years; Male:Female  
17 = 51:29) were evaluated, and the results are summarized in Table 1. The 31 anti-TNF $\alpha$  treatments  
18 consisted of 17 patients for IFX and 14 patients for ADA. The 23 anti-IL23 treatments consisted

1 of 14 patients for UST and 9 patients for GUS. The 26 anti-IL17 treatments consisted of 9 patients  
2 for SEC, 6 patients for IXE, and 11 patients for BRO. Psoriatic arthritis (PsA) patients were found  
3 the most frequently in anti-TNF $\alpha$  group (58.1%), followed by the anti-IL23 group (43.5%) and  
4 the anti-IL-17 group (38.5%). In the anti-TNF $\alpha$  group, 54.8% of the patients had a history of  
5 methotrexate (MTX) administration. After the biologics treatments started, the IFX group showed  
6 significantly elevated KL-6 (170.9%,  $p=0.014$ ) and the ADA group also tended to show elevated  
7 KL-6 (122.4%,  $p=0.051$ ), but the ADA results were not statistically significant. No other  
8 treatments showed significant elevation of KL-6. Regarding the targeting of cytokines, the anti-  
9 TNF $\alpha$  treatments resulted in significantly increased KL-6 (146.6%,  $p=0.002$ ). Next, we evaluated  
10 the ratio of change in KL-6 after treatment of with biologics. 13 of 17 the patients (75.6%) who  
11 were treated with IFX demonstrated at least a 25% increase in KL-6 level. In contrast, no other  
12 treatments, including ADA, showed any high ratios of change. In the total anti-TNF $\alpha$  group, 17  
13 of 31 the patients (54.8%) showed at least a 25% increase in KL-6 level. Serum KL-6 was above  
14 the normal cutoff (500 U/ml) in 3 patients before treatment and in 7 patients after treatment. Four  
15 patients—1 for IFX (1547 U/ml), 2 for GUS (988 U/ml), and 2 for SEC (519 U/ml, and 743  
16 U/ml)—had KL-6 >500U/ml before treatment. In the anti-TNF $\alpha$  group, 4 IFX patients and 1 ADA  
17 patient showed increased KL-6 after treatment. The changes in KL-6 for each patient who  
18 underwent anti-TNF $\alpha$  treatment are shown in Figure 1.

1

2 Changes in serum KL-6 in 7 patients

3 The patients with KL-6 &gt;500 U/ml are detailed in Figure 2. KL-6 increased slowly under

4 treatment with ADA (case 1), IFX (case 4) and SEC (case 7). Case 2 was treated for pneumocystis

5 pneumonia, and IFX was introduced after the pneumonia treatment had finished. KL-6 quickly

6 decreased to the normal range. Case 3 showed mild interstitial pulmonary changes by CT scan

7 before IFX treatment. After the IFX treatment started, KL-6 increased by several times, but a CT

8 scan showed no apparent interstitial changes. KL-6 was increased to 988 U/ml and 743 U/ml in

9 case 5 and case 6, after which we replaced the IFX with GUS and SEC, respectively. In case 5, a

10 CT scan showed no pulmonary changes at the highest KL-6. After the change to GUS, KL-6

11 quickly decreased to the normal range. In case 6, KL-6 decreased after the change to SEC. The

12 patient had pleurisy with SEC treatment (black arrow), and KL-6 was slightly elevated after the

13 pleurisy. Case 4 and case 5 had a history of MTX administration; the MTX was started 17 months

14 before the IFX in case 4, and 6 months after the IFX in case 5. ILD was not detected by CT scan

15 or chest X-ray in any of the patients who demonstrated elevated KL-6.

16

17 **Discussion**

18 We retrospectively reviewed the medical records of psoriasis patients treated with

1 biologics at our department. Consistent with previous reports<sup>8-11</sup>, anti-TNF $\alpha$  agents were found  
2 to significantly induce increases in KL-6. In our study, both UST and GUS were found to pose  
3 less risk of this. In addition, it is a first evidence that our study demonstrated that IXE and BRO  
4 have no impact on serum KL-6 level.

5         A previous study found that 55% of psoriasis patients undergoing anti-TNF $\alpha$  treatment  
6 showed serum KL-6 elevated by 20% or more from the baseline<sup>11</sup>. Furthermore, it was reported  
7 that approximately 10-20% of rheumatoid arthritis (RA) patients receiving anti-TNF $\alpha$  agents  
8 show increased serum KL-6<sup>1,13,14</sup>. Our study found a statistically significant increase in serum  
9 KL-6 during anti-TNF $\alpha$  treatment. 2 out of 7 patients were switched from IFX to other biologics,  
10 after which serum KL-6 quickly decreased to the normal range (Figure 2, case 5 and case 6).  
11 However, several patients demonstrated decreases in serum KL-6 under anti-TNF $\alpha$  treatment.  
12 Decreases in serum KL-6 during anti-TNF $\alpha$  treatment have also been reported in rheumatoid  
13 arthritis and psoriasis patients<sup>1,13</sup>. The causal mechanism behind ILD from anti-TNF $\alpha$  agents  
14 remains unclear. Several previous studies demonstrated the elevation of TNF $\alpha$ -converting  
15 enzyme (TACE) in psoriasis patients<sup>15</sup>. TACE enhances soluble TNF $\alpha$  from membrane TNF $\alpha$ ;  
16 however, TACE sheds the ectodomain of MUC1<sup>6</sup>. In addition to anti-TNF $\alpha$  agents, MTX is well  
17 known as a risk factor for ILD. As expected, MTX administration was highly associated with PsA.  
18 In this study, a significantly higher number of patients in the anti-TNF $\alpha$  group have a history of

1 MTX administration than those in the other treatment groups. The mean rate of change for KL-6  
2 level in IFX with MTX is higher than that of IFX without MTX, but this difference is not  
3 significant.

4 There are several limitations to this study. We did not consider the comorbidities. Some  
5 comorbidities, especially inflammatory bowel disease and uveitis, strongly influence the selection  
6 of biologics for psoriasis patients and also may be associated with ILD.

7 This study has shown the degree to which anti-TNF $\alpha$  agents, especially IFX, cause  
8 serum KL-6 to increase. However, such increases with anti-TNF $\alpha$  therapies do not seem to be  
9 directly associated with clinical ILD in most cases. In addition, several factors such as disease  
10 type, MTX administration and comorbidities may influence serum KL-6 level. To resolve this  
11 issue, basic research and prospective clinical research should be conducted.

12

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2

3

4

1 **Figure legend**

2

3 Figure 1 Changes in serum KL-6 levels after anti-TNF $\alpha$  treatments

4 The dotted line indicates the normal limit.

5 \* One patient was omitted from the graph but not from the table due to particularly high serum KL-6  
6 before IFX treatment (1,547 U/ml before IFX treatment, and 324 U/ml after).

7

8 Figure 2 Changes in serum KL-6 level with time course in representative patients

9 Serial serum KL-6 levels are shown in the graph for patients with >500 U/ml. In case 5 and case 6, the  
10 first biologic was replaced by a different one during the course (red line). Case 6 had pleurisy during  
11 SEC treatment (black arrow). MTX was started 17 months before IFX in case 4, and 6 months after  
12 IFX in case 5.

13

KL-6 in psoriasis with biologics

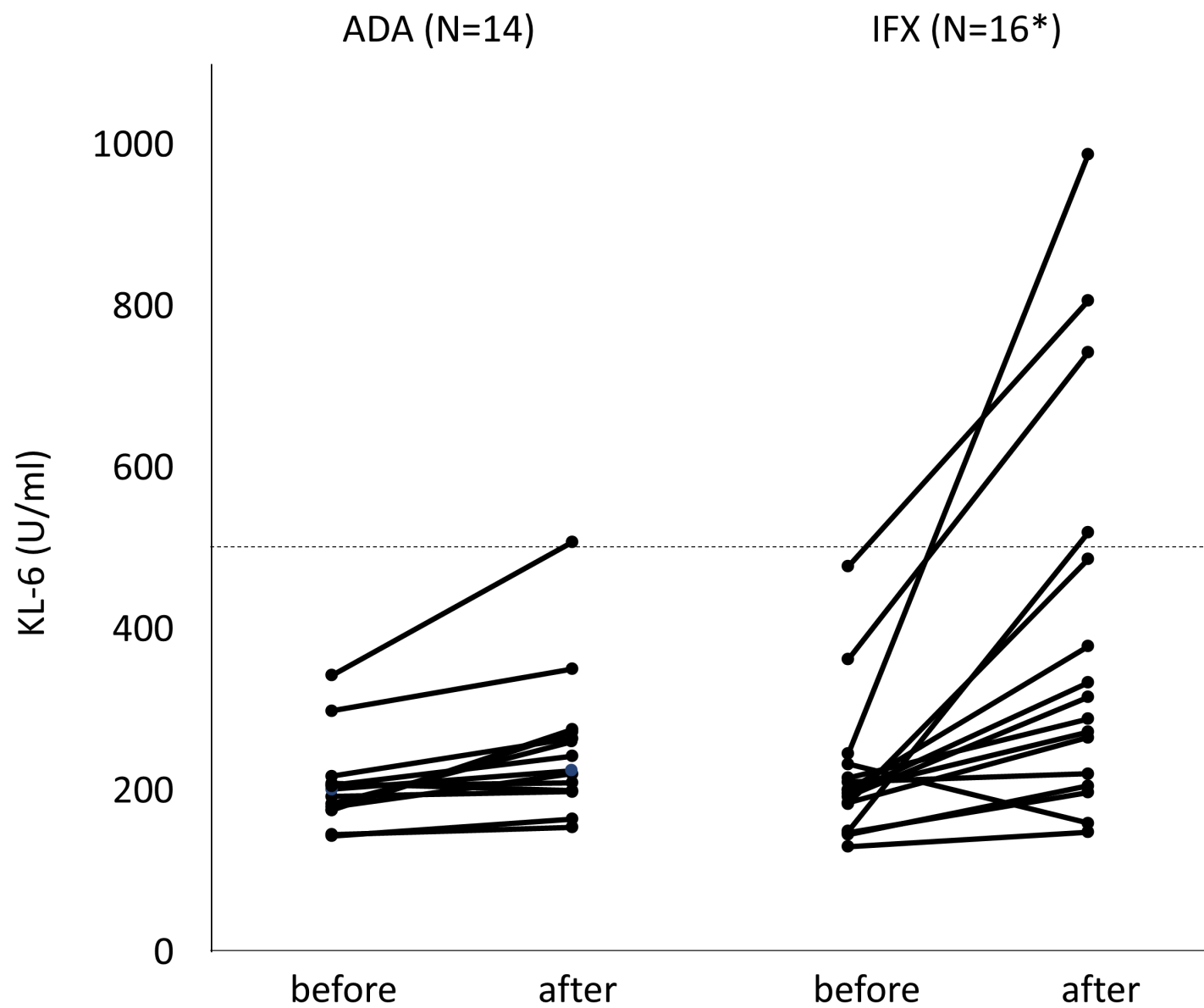
Treatment	N	PsA N(%)	Median age (range)	Gender M:F	MTX N (%)	Mean KL-6 (U/ml)		Mean rate of change (SD)	≥125% N (%)	After
						Before (SD)	After (SD)			≥500 U/ml N (%)
<b>IFX</b>	17	10 (58.8%)	50 (27-70)	12:5	11 (64.7%)	295.9 (333.4)*	391.8 (243.0)#	170.9% (93.7)	13(76.5%)	4 (23.5%)
<b>ADA</b>	14	8 (57.1%)	50 (29-80)	8:6	6 (35.3%)	205.9 (54.2)	253.7 (88.8)	122.4% (20.2)	4 (28.6%)	1 (7.1%)
<b>UST</b>	14	6 (42.9%)	64 (38-79)	8:6	2 (14.3%)	201.5 (40.5)	237.9 (86.1)	116.7% (24.7)	5 (35.7%)	
<b>GUS</b>	9	4 (44.4%)	59 (52-78)	6:3	3 (33.3%)	317.3 (256.4)*	260.9 (63.3)	102.3% (32.4)	2 (22.2%)	
<b>SEC</b>	9	3 (33.3%)	56 (41-74)	7:2	2 (22.2%)	287.4 (205.5)*	293.9 (181.2)	107.6% (22.8)	3 (33.3%)	1 (11.1%)
<b>IXE</b>	6	4 (66.7%)	66.5 (62-78)	2:4	0 (0%)	202.4 (45.7)	211.2 (87.3)	107.3% (29.8)	1 (16.7%)	
<b>BRO</b>	11	3 (27.3%)	47 (32-76)	8:3	1 (9.1%)	217.6 (61.7)	241.6 (56.6)	114.4% (20.7)	3 (27.2%)	
<b>Total</b>	80	38 (47.5%)	57 (27-80)	51:29	25 (31.3%)	246.5 (192.6)	280.8 (151.2)	125.5 (53.1)	31 (38.8%)	
<b>TNF</b>	31	18 (58.1%)	50 (27-80)	20:11	17 (54.8%)	250.9 (250.3)	322.7 (199.5)#	146.6% (73.9)	17 (54.8%)	5 (16.1%)
<b>IL23</b>	23	10 (43.5%)	59 (38-79)	14:9	5 (21.7%)	259.4 (168.0)	249.4 (77.3)	109.5% (28.2)	7 (30.4%)	
<b>IL17</b>	26	10 (38.5%)	60.5 (32-78)	17:9	3 (11.5%)	235.8 (130.5)	248.9 (120.0)	109.7% (23.0)	7 (26.9%)	1 (3.8%)

1 Table 1 Overall results of serum KL-6 levels in psoriasis patients under treatment with biologics

2

3 \* Four patients, one IFX, one GUS and two SEC, showed >500 U/ml of serum KL-6 level before

4 starting treatments. # p<0.05



\* One patient deleted due to extremely high score before IFX treatment.

