A Patient with KL-6 Elevation with Anti-TNF α Who Could Receive Long-Term Use without Interstitial Pneumonia after Class Switch of Anti-TNF α

Takuya Masuda^a Atsushi Yoshida^a Fumiaki Ueno^a Shintaro Hara^a
Haruaki Nabeta^a Shotaro Umezawa^a Mayuki Shirai^a Yoshihide Morikawa^a
Toshio Morizane^a Yutaka Endo^a Toshifumi Hibi^b

^aCenter for Gastroenterology and Inflammatory Bowel Disease, Ofuna Chuo Hospital, Kamakura, Japan; ^bCenter for Advanced IBD Research and Treatment, Kitasato Institute Hospital, Tokyo, Japan

Keywords

Interstitial lung disease · anti-TNF α · Inflammatory bowel disease · Ulcerative colitis · Crohn's disease

Abstract

A 40-year-old man with refractory ulcerative colitis (UC) was treated with tumor necrosis factor α inhibitor (anti-TNF α), infliximab. One month later, the chest computed tomography and laboratory test showed noninfectious interstitial lung disease (ILD) and elevation of serum Krebs von den Lungen-6 (KL-6). Fortunately, ILD disappeared after the discontinuation with anti-TNF α . Two and a half years after his first UC treatment, he was treated again with another anti-TNF α , adalimumab, for relapse and he had a second ILD. This course suggested anti-TNF α induced ILD. The characteristics of anti-TNF α -induced ILD in inflammatory bowel disease (IBD) are not well understood. We summarized and investigated the characteristics of such patients based on a literature review including 15 cases. It suggested that anti-TNF α -induced ILD in IBD might be rare and tends to have a better outcome compared with ILD in rheumatoid arthritis.

© 2019 S. Karger AG, Basel

Introduction

The anti-tumor necrosis factor α inhibitor (anti-TNF α) is an effective therapy for patients with moderately severe ulcerative colitis (UC) and Crohn's disease patients who fail to respond to conventional therapy [1]. However, one of the adverse events of anti-TNF α , such as interstitial lung disease (ILD), could be a clinical problem. Little is known about anti-TNF α -induced ILD among inflammatory bowel disease (IBD) patients, although more cases about anti-TNF α -induced ILD were reported [2–4] in other disease fields. Here we present a rare Japanese case of UC with ILD. We describe the details of our patient and summarize past case reports in order to compare the characteristics, treatments, and clinical courses among IBD patients with ILD induced by anti-TNF α .

Case Report

A 40-year-old man with nonsmoker and no history of lung disease, was admitted to our hospital in November 2010 because of a moderately severe exacerbation of his 3-year history of UC. He had been taking azathioprine (AZA) 100 mg/day and mesalazine 4 g/day since 2008. He received 1st infusion of anti-TNF α (infliximab

Fig. 1. Chest computed tomography after treatment with anti-TNF α showed diffuse ground-glass opacities with traction bronchiectasis in both middle lobes (a) and lower lobes (b).

[IFX]; 5 mg/kg) and achieved clinical remission at the time of discharge.

However, 1 month after the 2nd infusion of IFX 5 mg/kg, he visited our hospital because of 2 weeks history of low-grade fever, nonproductive cough, and fatigue. Fine crackle was auscultated in bilateral lungs and pulse oximetry was 96% (room air). Laboratory test showed white blood cell count of 4,580/mm³, neutrophil count 2,480/mm³, hemoglobin 10.7 g/dL, hematocrit 34.8%, serum LD 270 U/L, serum albumin 4.2 g/dL, and C-reactive protein 2.15 mg/dL. Chest X-ray and chest computed tomography (CT) showed non-segmental ground-glass opacity and traction bronchiectasis in bilateral lower lung fields. No findings of honeycomb shadows, mediastinal or both hilar lymphadenopathy, or pleural fluid in bilateral lung fields were seen (Fig. 1). Serum Krebs von den Lungen-6 (KL-6) levels were elevated at 1,820 U/mL, while there was normal range of surfactant protein-D (SP-D) and negativity for serum β -D-glucan, anti-*Mycoplasma pneumoniae* antibody, PCR assay for *Pneumocystis jirovecii* of his sputum, and cytomegalovirus antigenemia assay. IFX was discontinued due to suspected drug-induced ILD. He was prescribed prednisolone (PSL) 30 mg/day and tapering down into 0 mg/day for 6 months. Fortunately, remission with maintenance therapy for 2 years has been carried out without exacerbation of UC. Serum KL-6 levels had returned to the normal range after the discontinuation with IFX. Chest CT showed the disappearance of ground-glass opacity.

He (42-year-old man) had relapse of UC and was admitted to the hospital 2 years after remission. Endoscopic appearance was severe UC (Mayo endoscopic subscore 3). He had been taking AZA 100 mg/day and mesalazine 4 g/day since 2008; however, his clinical symptom became worse. Other types of anti-TNF α (adalimumab [ADA]) (160-80-40 mg) had started since December 2013. Once again, his serum KL-6 level elevated to 1,742 U/mL on March 2014 and kept a high level from 1,000 to 3,000 U/mL during treatment with ADA. But at this time, ADA was continued with carefully keeping consultation with a respiratory specialist, because he had desired to continue ADA, which maintained remission in UC,

and ILD had not occurred in clinical symptom and CT image finding.

Two and a half years after ADA maintenance therapy, he (44-year-old man) had developed ILD again and laboratory test showed high level of serum KL-6 1,158 U/L and SP-D 159.9 ng/dL. ILD was mildly active at this time and chest CT showed minor ground-glass opacity and linear opacities in bilateral lower lung fields. This ILD improved and serum KL-6 and SP-D returned to the normal range promptly by PSL (30 mg/day), even while continuing ADA administration and tapering down to PSL free. He has been continuing ADA for remission treatment of UC.

Discussion

This is the case report of not only developing drug-induced ILD after induction of IFX and ADA, two different types of anti-TNF α , but also preceding the elevation of serum KL-6 level before the second onset of ILD after induction of ADA. Favorable complete remission of UC could be gained by anti-TNF α ; however, a recent case report showed a fatal adverse effect in ILD induced by the drugs [5]. Although TNF α -induced ILD could occur among patients with various autoimmune diseases, there are few studies of anti-TNF α -induced ILD in IBD field. Thus, we summarized the previous case reports and studies of anti-TNF α agents inducing ILD among IBD patients [5–14].

The prevalence of respiratory adverse effects of IFX among 484 UC patients was reported to be 3.5% (17/484), including 1 pneumonia, 1 tuberculosis, and 1 histoplasma

Table 1. Summary of available IBD Cases with ILD induced by anti-TNF α

Case	First author, year [ref.]	Age, years	Sex	IBD type	Disease years (IBD)	Pre-LD	Symptom
1	Rofaief, 2017 [5]	53	m	UC	11	tuberculosis	severe dyspnea
2	Numakura, 2016 [6]	23	m	CD	1	N/A	dry cough, itchy eruption, bilateral hilar lymphadenopathy
3	Lee, 2015 [7]	58	m	CD	0.3	never	dyspnea
4	Lee, 2015 [7]	51	f	UC	11	never	dry cough, dyspnea
5	Lee, 2015 [7]	48	f	UC	9	never	cough, dyspnea, fever
6	Lee, 2015 [7]	37	m	UC	10	never	dyspnea
7	Lee, 2015 [7]	39	f	UC	0.7	never	dyspnea, fever
8	Lee, 2015 [7]	74	f	UC	5	never	dyspnea, fever
9	Kohnno, 2015 [8]	67	f	CD	6	never	dry cough, chest pain
10	Casanova, 2015 [9]	59	f	CD	2	smoker	dyspnea, cough, and fatigue
11	Caccaro, 2013 [10]	25	f	CD	9	never	shortness of breath and fatigue
12	Reid, 2011 [11]	45	m	CD	0.5	smoker	fever, chills, diaphoresis, nonproductive cough, exertional dyspnea, and bloody diarrhea
13	Wiener, 2008 [12]	63	f	UC	10	smoker	dyspnea, dry cough
14	Weatherhead, 2006 [13]	22	f	CD	2	N/A	cough, breathlessness
15	Sen, 2012 [14]	29	f	UC	0.3	asthma	dyspnea
16	Our case	40	m	UC	3	never	dry cough and fatigue

Case	Anti-TNF	ILD onset duration after anti-TNF α therapy	Other drugs	Therapy for ILD	Outcome
1	infliximab	16 weeks	5-ASA, PSL	continue anti-TNF α	dead
2	infliximab	14 weeks	PSL, 5-ASA	continue anti-TNF α	resolved spontaneously
3	adalimumab	4 weeks	5-ASA	stop anti-TNF α , start steroid	improved after 26 week (CXR)
4	infliximab	6 weeks	5-ASA	stop anti-TNF α , start steroid	improved after 4 weeks (CXR)
5	infliximab	14 weeks	5-ASA	stop anti-TNF α , start steroid	improved after 13 weeks (CXR)
6	infliximab	6 weeks	none	stop anti-TNF α , start steroid	improved after 6 weeks (CXR)
7	infliximab	6 weeks	AZA	stop anti-TNF α	improved after 1 week (CXR)
8	adalimumab	8 weeks	5-ASA	stop anti-TNF α	improved after 17 weeks (CXR)
9	infliximab $\rightarrow$ adalimumab	14 weeks	AZA	continue anti-TNF α , start steroid	improved after 1 week (CXR), KL-6 $\downarrow$, mucosal healing
10	adalimumab	4 weeks	AZA	stop anti-TNF α , start steroid	normalization of spirometry after 12 weeks
11	adalimumab $\rightarrow$ infliximab	16 weeks	5-ASA, PSL, AZA	stop anti-TNF α , start steroid	improved after 10 weeks (CT)
12	adalimumab	40 weeks	PSL, MTX	stop anti-TNF α , start steroid	clinical and CXR improvement within 8 weeks and restart methotrexate
13	infliximab	24 weeks	PSL, 5-ASA, AZA	start steroid	clinical improvement within 6 weeks
14	infliximab	2 weeks	5-ASA, AZA	stop anti-TNF α , start steroid	normalization of spirometry after 2 weeks
15	infliximab	2 weeks	none	stop anti-TNF α , start steroid	improved after 12 weeks (CT)
16	infliximab $\rightarrow$ adalimumab	6 weeks	5-ASA, AZA	1. stop anti-TNF α , start steroid 2. continue anti-TNF α , start steroid	improved after 24 weeks (CXR) improved after 8 weeks (CT)

Table 2. The biologic therapy with elevated KL-6 values and the progression of ILD

First author, year [ref.]	Biologic therapy with elevated KL-6	Progression of ILD with abnormal KL-6 values
Takahashi, 2014 [29]	infliximab 11.2%, etanercept 4.4%, adalimumab 22.2%, tocilizumab 0% on RA	anti-TNF α ILD events 20.0%
Horigai, 2013 [30]	infliximab 15.6%, certolizumab pegol 7.8%, golimumab 1.8% on RA	no apparent ILD
Takamura, 2013 [31]	infliximab, etanercept, adalimumab, and tocilizumab 17.9% on RA	no apparent ILD
Koiwa, 2012 [32]	adalimumab 10.3% on RA	no apparent ILD
Hayashi, 2017 [27]	infliximab or adalimumab 55% on psoriasis	no apparent ILD

(dead) from the result of ACT trial [15]. However, non-infectious lung disease, such as ILD, might be a rare adverse effect among UC patients using anti-TNF α because neither noninfectious ILD nor elevation of KL-6 were reported among these patients, while the prevalence of anti-TNF α -induced ILD is reported to be 0.5–0.6% in rheumatoid arthritis (RA) [16].

The demographic and clinical characteristics of 16 IBD patients including our patient are summarized in Table 1. The average age was 49 ± 15 years (mean $\pm$ SD), and 10 of 16 patients (63%) were female. The tendency of clinical features was a mature woman in the early period (5.4 ± 4.3 years) of IBD, regardless of any types of IBD (UC9:CD7). None of the association was seen with the history of previous lung disease such as smoking or autoimmune disease, which was not seen in our patient. However, he rapidly developed anti-TNF α -induced ILD so that it is difficult to predict appearance of the ILD from their history. The remarkable characteristics of clinical symptoms were dyspnea (13/16), cough (9/16), and fever (4/16). Thus, these clinical symptoms are important to make an early diagnosis of anti-TNF α agent-induced ILD (Table 1).

In IBD patients with noninfectious ILD, IFX was more reported (IFX:ADA, 10:5) in the past cases (Table 1). Our patient developed ILD 1 month after IFX (chimeric antibody) induction. Previously, lung toxicity by ADA (complete human antibody) was controversial. However, our patient recurred with ILD caused by ADA after 2.5 years. According to the past case report [17], as example of the case of ADA-induced ILD in RA, ADA could be a risk of ILD.

IBD patients have a tendency to shorter periods of developing ILD after induction of anti-TNF α than other autoimmune diseases because the average ($\pm$ SD) was 13.0 ± 10.4 weeks among IBD patients and 26.3 ± 5.3 weeks among patients with other autoimmune diseases [3] (Table 1), whereas our patient had 6 weeks to the first onset and 2.5 years to the second onset of ILD.

5-ASA or AZA as combined drugs of anti-TNF α were used at a high rate (Table 1). However, these drugs or IBD itself were known to cause ILD, especially lymphocyte infiltration or fibrosis on interstitial tissue of lung [18]. Remarkably, almost all these case series did not develop ILD until induction of anti-TNF α agent, despite long-term administration of 5-ASA or AZA, and this fact indicates that anti-TNF α might have some pathogenic effect of developing IDL or exacerbating latent ILD lesions caused by other drugs of IBD or IBD itself. In our patient, ILD was not recurrent during off-terms of anti-TNF α agent with the use of 5-ASA and AZA.

The mechanism of anti-TNF α -induced ILD is still unclear [19, 20]. Past studies showed that anti-TNF α improves ILD as well as exacerbates it among patients with various autoimmune disease [2, 21], whereas recent studies showed a part of the mechanisms of how anti-TNF α could promote automatic inflammatory response. Some basic research revealed that anti-TNF α antibody could inhibit membrane TNF receptor 2, which is needed for inducing apoptosis of activated inflammatory cells [22], and activate TNF receptor 2-positive pathogenic T cells through anti-TNF α antibody and TNF receptor 2 complex [23]. These data may explain why both IFX and ADA, two different types of anti-TNF α , caused ILD in our patient.

Elevation of KL-6 during occurrence or recurrence of ILD induced by two different anti-TNF α was remarkable in our patient. KL-6 is one of the common ILD serum markers and exists on the membrane of type 2 alveolar epithelium, and elevation of serum KL-6 indicates destruction or reproduction of type 2 alveolar epithelium, or increased permeability of alveolar capillary barrier from any cause [24].

One study showed that a serum KL-6 level of over 2,750 U/mL was associated with poor outcome among patients with ILD due to idiopathic or collagen disease [25]. Moreover, a study of 30 cases of drug-induced ILD due to various drugs (excluding anti-TNF α) showed that

elevation of KL-6 was associated with more serious types of diffuse alveolar damage pattern or chronic interstitial pneumonia pattern, and not with mild type of bronchiolitis obliterans organizing pneumonia/eosinophilic pneumonia or hypersensitivity pneumonitis pattern [26]. According to these data, a high level of serum KL-6 might predict poor outcome in patients with ILD.

However, 52% of psoriasis patients treated with IFX or ADA experienced increase of serum KL-6 without developing ILD. Furthermore, spontaneous decrease in serum KL-6 was seen among some psoriasis patients treated with anti-TNF α [27, 28]. In some RA patient, serum KL-6 elevated during use of anti-TNF α and decreased after withdrawing its agent [29–32] (Table 2). According to the clinical trial of anti-TNF α in RA, 11.2%, 4.4%, 22.2%, and 0% of RA participants treated with IFX, etanercept, ADA, and tocilizumab, respectively, experienced elevation of serum KL-6 (≥ 500 U/mL) [29]. Similar findings were seen in trials with IFX (15.6 %), certolizumab pegol (7.8%), and golimumab (1.8%) [30], and the progression of ILD with abnormal KL-6 value was very low. KL-6 elevation tends to be lower in human or humanized monoclonal antibody (golimumab, tocilizumab) than in chimeric antibody (IFX) (Table 2). In our case, a high level of serum KL-6 was seen during the first ILD and preceded the onset of the second ILD. Hence, elevation of serum KL-6 during induction of anti-TNF α could be useful for diagnosis or prediction of ILD but not necessarily for prediction of poor outcome.

In most IBD cases, ILD was treated with steroids and withdrawing anti-TNF α agents. The average period of improving ILD was 8.2 ± 10.5 weeks ($\pm$ SD) (Table 1). However, some cases tried to continue ADA with combination of steroid in the second onset of ILD, like in our case [7, 10–14, 17].

The association with mortality risk due to anti-TNF α agent-induced ILD seems to be old age (above 65 years old), frequent use of immunosuppressive drugs, and rapid diagnosis of ILD [3]. Regarding severity or lethality, IBD cases with anti-TNF α agent-induced ILD tended to have better outcome than various autoimmune diseases.

Only one patient died during rapid induction of IFX in UC [5], while 15 of 52 RA patients with ILD [3]. Hence, careful investigation of ILD symptoms such as dyspnea or dry cough and rapid treatment are important when starting anti-TNF α in IBD patients. Our case succeeded to continue UC remission maintenance without withdrawing ADA by temporally combining PSL.

Conclusion

We reported a rare UC case of anti-TNF α -induced ILD and summarized the literature and our case including 16 IBD case reports. Clinicians should recognize the risk of anti-TNF α -induced ILD, which tends to have a better outcome by stopping anti-TNF α or using steroid. Elevation of serum KL-6 during anti-TNF α treatment could be useful to remind the risk of developing ILD but not necessarily for prediction of poor outcome.

Statement of Ethics

The study was performed in accordance with the ethics guidelines in Japan. This report did not need to be approved by the institution's ethics committee. Patient's informed consent was obtained.

Disclosure Statement

There is no conflict of interest.

Author Contributions

A. Yoshida, F. Ueno designed the study. The data were collected by T. Masuda, A. Yoshida. T. Masuda, A. Yoshida, T. Morizane analyzed the data. T. Masuda, A. Yoshida drafted the manuscript. T. Masuda, A. Yoshida, S. Hara, H. Nabeta, S. Umezawa, M. Shirai, Y. Morikawa, Y. Endo interpreted the data, and T. Hibi made critical revisions to the manuscript. All authors reviewed and approved the final version of manuscript.

References

- 1 Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2011 Apr;106(4):644–59.
- 2 Khasnis AA, Calabrese LH. Tumor necrosis factor inhibitors and lung disease: a paradox of efficacy and risk. *Semin Arthritis Rheum*. 2010 Oct;40(2):147–63.
- 3 Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, Pego-Reigosa JM, Retamozo S, Bove A, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. *Semin Arthritis Rheum*. 2011 Oct;41(2):256–64.

- 4 Hagiwara K, Sato T, Takagi-Kobayashi S, Hasegawa S, Shigihara N, Akiyama O. Acute exacerbation of preexisting interstitial lung disease after administration of etanercept for rheumatoid arthritis. *J Rheumatol*. 2007 May; 34(5):1151–4.
- 5 Rofaiei R, Kohli S, Mura M, Hosseini-Moghaddam SM. A 53-year-old man with dyspnoea, respiratory failure, consistent with infliximab-induced acute interstitial pneumonitis after an accelerated induction dosing schedule. *BMJ Case Rep*. 2017 May;2017:12.
- 6 Numakura T, Tamada T, Nara M, Muramatsu S, Murakami K, Kikuchi T, et al. Simultaneous development of sarcoidosis and cutaneous vasculitis in a patient with refractory Crohn's disease during infliximab therapy. *BMC Pulm Med*. 2016 Feb;16(1):30.
- 7 Lee HS, Jo KW, Shim TS, Song JW, Lee HJ, Hwang SW, et al. Six Cases of Lung Injury Following Anti-tumour Necrosis Factor Therapy for Inflammatory Bowel Disease. *J Crohn's Colitis*. 2015 Nov;9(11):1053–7.
- 8 Kohn H, Okada H, Hiraoka S, Tanaka T. [A case of asymptomatic Sjögren's syndrome who developed interstitial pneumonia during monoclonal antibody therapy of Crohn's disease]. *Nihon Shokakibyo Gakkai Zasshi*. 2015 Jul;112(7):1326–33.
- 9 Casanova MJ, Chaparro M, Valenzuela C, Cisneros C, Gisbert JP. Adalimumab-induced interstitial pneumonia in a patient with Crohn's disease. *World J Gastroenterol*. 2015 Feb;21(7):2260–2.
- 10 Caccaro R, Savarino E, D'Inca R, Sturniolo GC. Noninfectious interstitial lung disease during infliximab therapy: case report and literature review. *World J Gastroenterol*. 2013 Aug;19(32):5377–80.
- 11 Reid JD, Bressler B, English J. A case of adalimumab-induced pneumonitis in a 45-year-old man with Crohn's disease. *Can Respir J*. 2011 Sep-Oct;18(5):262–4.
- 12 Wiener CM, Muse VV, Mark EJ. Case records of the Massachusetts General Hospital. Case 33-2008. A 63-year-old woman with dyspnea on exertion. *N Engl J Med*. 2008 Oct;359(17):1823–32.
- 13 Weatherhead M, Masson S, Bourke SJ, Gunn MC, Burns GP. Interstitial pneumonitis after infliximab therapy for Crohn's disease. *Inflamm Bowel Dis*. 2006 May;12(5):427–8.
- 14 Sen S, Peltz C, Jordan K, Boes TJ. Infliximab-induced nonspecific interstitial pneumonia. *Am J Med Sci*. 2012 Jul;344(1):75–8.
- 15 Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005 Dec; 353(23):2462–76.
- 16 Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *Ann Rheum Dis*. 2008 Feb;67(2):189–94.
- 17 Komiya K, Ishii H, Fujita N, Oka H, Iwata A, Sonoda H, et al. Adalimumab-induced interstitial pneumonia with an improvement of pre-existing rheumatoid arthritis-associated lung involvement. *Intern Med*. 2011;50(7): 749–51.
- 18 Majewski S, Piotrowski W. Pulmonary manifestations of inflammatory bowel disease. *Arch Med Sci*. 2015 Dec;11(6):1179–88.
- 19 Hilary C. Cain: Drug-induced pulmonary disease due to nonchemotherapeutic agents. Fishman's pulmonary diseases and disorders fifth edition 2015; p945-992.
- 20 Kalliolias GD, Ivashkiv LB. TNF biology, pathogenic mechanisms and emerging therapeutic strategies. *Nat Rev Rheumatol*. 2016 Jan;12(1):49–62.
- 21 Nakashita T, Ando K, Kaneko N, Takahashi K, Motojima S. Potential risk of TNF inhibitors on the progression of interstitial lung disease in patients with rheumatoid arthritis. *BMJ Open*. 2014 Aug;4(8):e005615.
- 22 Blüml S, Binder NB, Niederreiter B, Polzer K, Hayer S, Tauber S, et al. Antiinflammatory effects of tumor necrosis factor on hematopoietic cells in a murine model of erosive arthritis. *Arthritis Rheum*. 2010 Jun;62(6):1608–19.
- 23 McCann FE, Perocheau DP, Ruspi G, Blazek K, Davies ML, Feldmann M, et al. Selective tumor necrosis factor receptor I blockade is antiinflammatory and reveals immunoregulatory role of tumor necrosis factor receptor II in collagen-induced arthritis. *Arthritis Rheumatol*. 2014 Oct;66(10):2728–38.
- 24 Ishikawa N, Hattori N, Yokoyama A, Kohno N. Utility of KL-6/MUC1 in the clinical management of interstitial lung diseases. *Respir Investig*. 2012 Mar;50(1):3–13.
- 25 Satoh H, Kurishima K, Ishikawa H, Ohtsuka M. Increased levels of KL-6 and subsequent mortality in patients with interstitial lung diseases. *J Intern Med*. 2006 Nov;260(5):429–34.
- 26 Ohnishi H, Yokoyama A, Yasuhara Y, Watanabe A, Naka T, Hamada H, et al. Circulating KL-6 levels in patients with drug induced pneumonitis. *Thorax*. 2003 Oct;58(10):872–5.
- 27 Hayashi M, Yanaba K, Umezawa Y, Asahina A, Nakagawa H. Impact of anti-tumor necrosis factor-α agents on serum levels of KL-6 and surfactant protein-D in patients with psoriasis. *J Dermatol*. 2017 Sep;44(9):1063–6.
- 28 Higashi Y, Tada K, Shimokawa M, Kawai K, Kanekura T. Elevation of serum KL-6 in patients with psoriasis treated with anti-tumour necrosis factor-α therapy. *Clin Exp Dermatol*. 2016 Jan;41(1):88–90.
- 29 Takahashi K, Nakamura H, Takenouchi K, Iizawa N, Koiwa M, Sato A, et al. Serum KL-6 elevation and possible pulmonary involvement in patients with rheumatoid arthritis treated with biological agents. *J Nippon Med Sch*. 2014;81(6):364–71.
- 30 Harigai M, Takamura A, Atsumi T, Dohi M, Hirata S, Kameda H, et al. Elevation of KL-6 serum 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 Mar;23(2):284–96.
- 31 Takamura A, Hirata S, Nagasawa H, Kameda H, Seto Y, Atsumi T, 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 Mar;23(2):297–303.
- 32 Koiwa M, Goto S, Takenouchi K, Takahashi K, Kamada T, Nakamura H. Elevation of serum KL-6 levels in 3 patients with rheumatoid arthritis treated with adalimumab. *Mod Rheumatol*. 2012 Feb;22(1):147–51.