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

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Abstract

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

Introduction

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

Several studies have investigated the influence of biologics on serum KL-6 levels[8–11]. We here retrospectively review KL-6 levels in psoriasis patients who received 7 different biological treatments.

Methods

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

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

Results

Serum KL-6 levels were found to be significantly elevated after anti-TNFα treatment

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

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

Changes in serum KL-6 in 7 patients

The patients with KL-6 >500 U/ml are detailed in Figure 2. KL-6 increased slowly under treatment with ADA (case 1), IFX (case 4) and SEC (case 7). Case 2 was treated for pneumocystis pneumonia, and IFX was introduced after the pneumonia treatment had finished. KL-6 quickly decreased to the normal range. Case 3 showed mild interstitial pulmonary changes by CT scan before IFX treatment. After the IFX treatment started, KL-6 increased by several times, but a CT scan showed no apparent interstitial changes. KL-6 was increased to 988 U/ml and 743 U/ml in case 5 and case 6, after which we replaced the IFX with GUS and SEC, respectively. In case 5, a CT scan showed no pulmonary changes at the highest KL-6. After the change to GUS, KL-6 quickly decreased to the normal range. In case 6, KL-6 decreased after the change to SEC. The patient had pleurisy with SEC treatment (black arrow), and KL-6 was slightly elevated after the pleurisy. Case 4 and case 5 had a history of MTX administration; the MTX was started 17 months before the IFX in case 4, and 6 months after the IFX in case 5. ILD was not detected by CT scan or chest X-ray in any of the patients who demonstrated elevated KL-6.

Discussion

We retrospectively reviewed the medical records of psoriasis patients treated with

biologics at our department. Consistent with previous reports[8–11], anti-TNFα agents were found to significantly induce increases in KL-6. In our study, both UST and GUS were found to pose less risk of this. In addition, it is a first evidence that our study demonstrated that IXE and BRO have no impact on serum KL-6 level.

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

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

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

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

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Figure legend

Figure 1 Changes in serum KL-6 levels after anti-TNFα treatments

The dotted line indicates the normal limit.

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

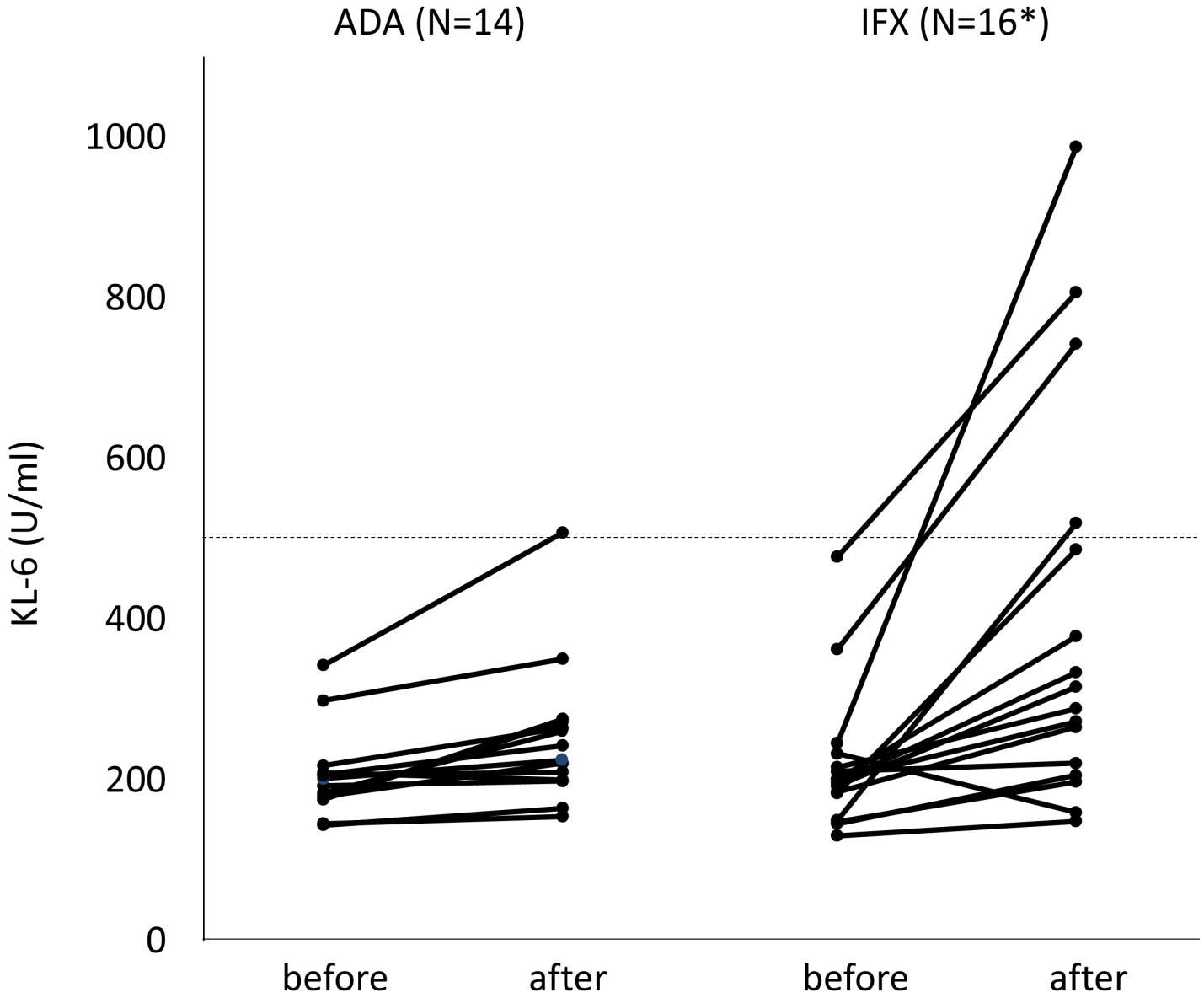
Figure 2 Changes in serum KL-6 level with time course in representative patients

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

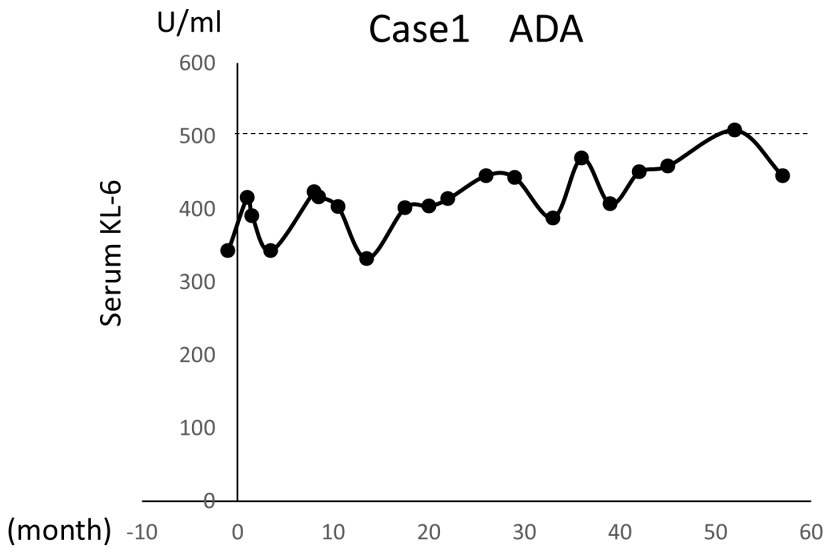
Treatment	N	PsA N(%)	Median age (range)	Gender M:F	MTX N (%)	Mean KL-6 (U/ml) Before (SD)	Mean KL-6 (U/ml) After (SD)	Mean rate of change (SD)	≧125% N (%)	After ≧500 U/ml N (%)
IFX	17	10 (58.8%)	50 (27-70)	12:5	11 (64.7%)	295.9 (333.4)*	391.8 (243.0)#	170.9% (93.7)	13(76.5%)	4 (23.5%)
ADA	14	8 (57.1%)	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%)
UST	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%)	
GUS	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%)	
SEC	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%)
IXE	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%)	
BRO	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%)	
Total	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%)	
TNF	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%)
IL23	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%)	
IL17	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%)

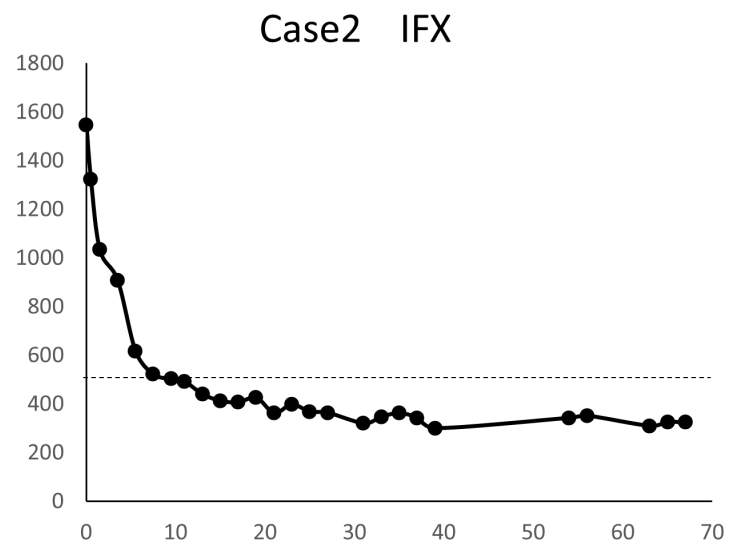
Table 1 Overall results of serum KL-6 levels in psoriasis patients under treatment with biologics

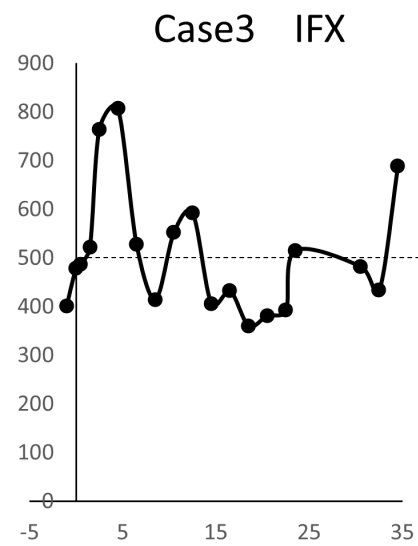
* Four patients, one IFX, one GUS and two SEC, showed >500 U/ml of serum KL-6 level before starting treatments. # $p<0.05$

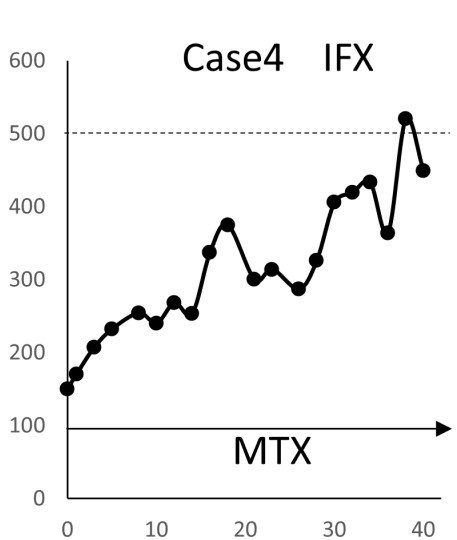


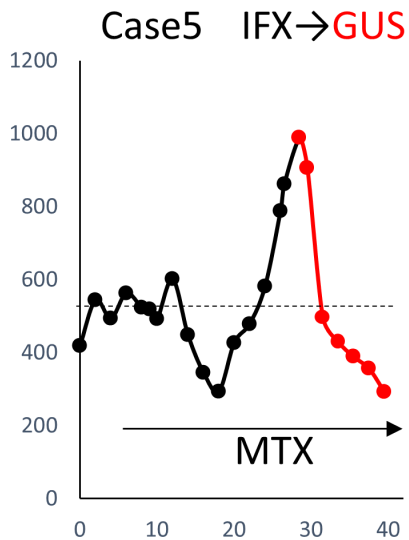
* One patient deleted due to extreamly high score before IFX treatment.

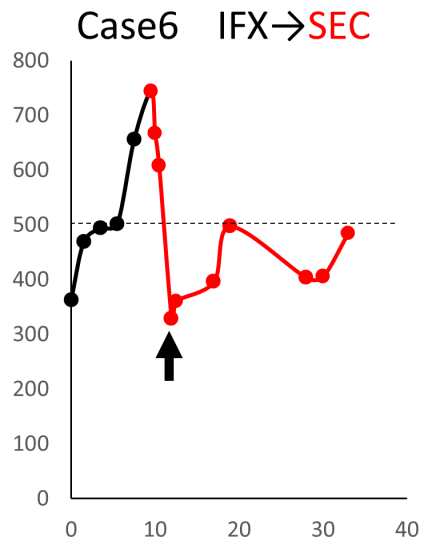

U/ml
Case1 ADA
Serum KL-6
600
500
400
300
200
100
0
(month)
-10
0
10
20
30
40
50
60

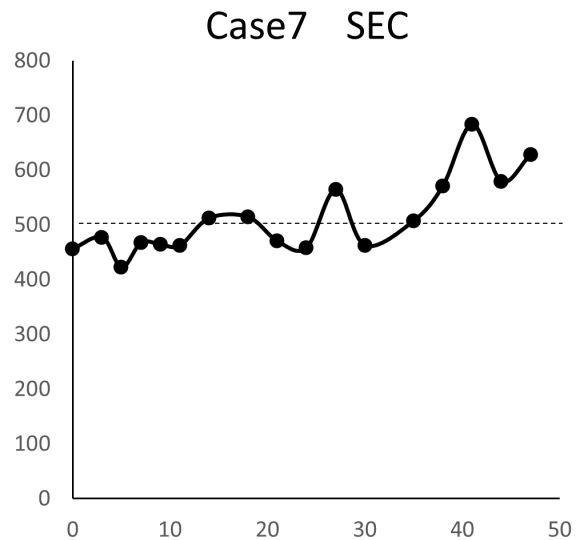

Case2 IFX
1800
1600
1400
1200
1000
800
600
400
200
0
0
10
20
30
40
50
60
70


Case3 IFX
900
800
700
600
500
400
300
200
100
0
-5
5
15
25
35


Case4 IFX
600
500
400
300
200
100
0
MTX
0
10
20
30
40


Case5 IFX→GUS
1200
1000
800
600
400
200
0
MTX
0
10
20
30
40


Case6 IFX→SEC
800
700
600
500
400
300
200
100
0
0
10
20
30
40


Case7 SEC
800
700
600
500
400
300
200
100
0
0
10
20
30
40
50