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Development of a New Treatment for Interstitial Lung Disease and COPD with Platinum-Palladium - In Relation to Improvement Examples and Research Examples

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Article

Development of a New Treatment for Interstitial Lung Disease and COPD with Platinum-Palladium. —In Relation to Improvement Examples and Research Examples-Title

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Abstract: Interstitial pneumonia is a general term for diseases in which inflammation occurs mainly in the interstitium of the lung. It is also pointed out that interstitial pneumonia reduces alveolar function and makes it difficult to take in oxygen through inspiration, causing symptoms such as dyspnea and coughing, which may eventually lead to respiratory failure. At present, there is no effective treatment and only conservative treatment exists. This time, we report that the therapeutic effect was confirmed in patients with interstitial pneumonia who took platinum-palladium. In this case, improvement tendencies were observed in patients with Idiopathic pulmonary fibrosis (IPF), but improvement tendencies were also observed in many other lung diseases. In order to explore the mechanism, AMPK was measured at the in vitro level, and blood KL-6 and hydrogen peroxide levels in the patient were measured at the in vivo level. AMPK values were significantly elevated by more than 800%, KL-6 and hydrogen peroxide levels were also significantly decreased by drinking platinum-palladium. Platinum-palladium exhibits a strong antioxidant effect and is the only substance in the world that can approach all four types of active oxygen. In addition, when it was actually administered to patients, there were cases of dramatic improvement, and it was confirmed that KL-6, a parameter of lung function, decreased in 16 out of 32 patients As the number of cases is expected to increase in the future, the substance is expected to be effective as a drug, although it is currently classified as a soft drink.

Keywords: Interstitial pneumonia; COPD; Platinum-palladium; Functional nutritional water; KL-6; AMPK; Hydrogen peroxide; Case improvement; Oxygen inhalation

1. Introduction

Interstitial pneumonia is a general term for diseases in which inflammation occurs mainly in the interstitium of the lungs [1]. Alveoli are roughly divided into parenchyma and interstitium, with the inside of the alveoli being called the parenchyma and the walls and surrounding tissues of the alveoli being called the interstitium. Interstitial pneumonia is called interstitial pneumonia when inflammatory changes occur in the interstitium [2]. Interstitial pneumonia with identifiable causes includes "autoimmune interstitial pneumonia," "occupational environment interstitial pneumonia," and "iatrogenic interstitial pneumonia," [3,4,5]and those with unidentifiable causes are called "idiopathic interstitial pneumonia" [6]. In addition, in the 2013 ATS/ERS classification of interstitial pneumonia, there are nine classifications:

(1) Major IIPs
1. Idiopathic pulmonary fibrosis (IPF)
2. Idiopathic nonspecific interstitial pneumonia (idiopathic NSIP)
3. Respiratory bronchiolitis interstitial lung disease (RB-ILD)

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4. Desquamative interstitial pneumonia (DIP)
5. Cryptogenic organizing pneumonia (COP)
6. Acute interstitial pneumonia (AIP)
(2) Rare IIPs
1. Idiopathic lymphoid interstitial pneumonia (LIP)
2. Idiopathic pleuroparenchymal fibroelastosis (PPFE)
(3) Unclassifiable
1. Unclassifiable IIPs [7].

In this study, we investigated the possibility of a new treatment for patients with idiopathic pulmonary fibrosis (IPF). In interstitial pneumonia, inflammation gradually causes fibrosis of the alveolar walls [8], and pulmonary surfactant protein-D (SP-D) levels increase [9,10]. As alveolar function declines, it becomes difficult to take in oxygen through inhalation, leading to respiratory symptoms such as shortness of breath and coughing, and it has been pointed out that this may ultimately lead to respiratory failure [11]. At present, there is no effective treatment, and the only symptomatic treatment is immunosuppressants for interstitial lung disease [12].

On the other hand, COPD (Chronic Obstructive Pulmonary Disease) is a type of chronic respiratory disease that causes alveolar destruction and inflammation, resulting in respiratory symptoms such as shortness of breath and progressing irreversibly. Smoking is the biggest risk factor for COPD in many cases, but it has been suggested that it may also be caused by other environmental pollution, etc. ［13,14］. As with interstitial pneumonia, there is no established effective treatment for COPD, and the only conservative treatment is oxygen inhalation and maintaining and improving quality of life [16]. Epidemiologically, it is said that by 2030, WHO predicts that COPD will be the third leading cause of death in the world [16]. Epidemiological studies have also suggested that COPD has a high risk of developing lung cancer [17]. Until now, smoking cessation, antioxidants, dietary therapy, and alternative therapies have been the focus for COPD [18], but these have been aimed at slowing down the progression. In our clinical experience, the administration of platinum-palladium to COPD patients has shown a tendency for symptoms to improve in approximately 40-50% of patients. For the above reasons, we expected that the same therapeutic effect would be seen in interstitial pneumonia, so we examined cases. Platinum palladium is generally sold as a soft drink (functional nutritional water) under the name PAPLAL®, which is a colloidal mixture of platinum and palladium (a solution of platinum and palladium mixed at a ratio of 1: 3) (Figure.1, 2) and was invented by Dr. Hideyo Noguchi. It is a completely new functional nutritional water that is expected to have various effects, such as inducing apoptosis in stomach and colon cancer and activating NK cells (unpublished).

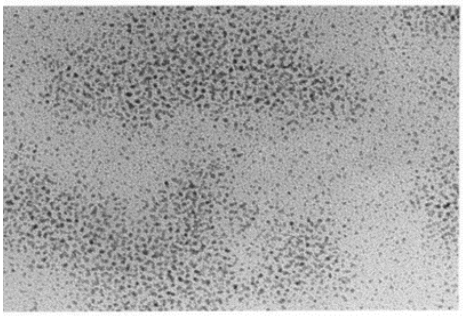

Figure 1. Platinum colloid.

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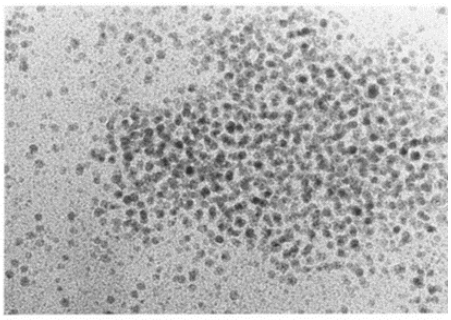

Figure 2. Palladium colloid.

Platinum is a chemically very stable element and is used for various purposes. In the medical field, its complexes are used as anticancer drugs [19]. Other usages focusing on the antioxidant properties of platinum have been reported [20]. Palladium is one of the platinum group elements and is widely used as a material for industrial products and dental treatment [21, 22]. It has also been reported that palladium has the effect of giving back reducing power to platinum involved in reduction reactions [23], and attempts have been made to use substances that are mixtures of platinum and palladium [24]. Due to the chemical reactions and specificities of the two elements, a mixture of platinum and palladium is expected to be useful as a substance with sustained antioxidant properties compared to platinum alone [24]. Furthermore, it has been found that platinum-palladium moderately removes all four types of active oxygen [25]. A literature survey showed that there is no other substance that removes all four types of active oxygen (generally considered to be superoxide anion radical, hydroxyl radical, hydrogen peroxide, and singlet oxygen) [26]. In addition, because platinum-palladium has a low absorption rate in the intestinal tract due to its characteristics [27,28], it is possible that it may act as a catalyst and activate AMPK (AMP-activated protein kinase) at the cellular level in the digestive tract, thereby contributing to the improvement of symptoms and lesions of interstitial pneumonia and COPD. Therefore, in this study, we reported cases and measured the amount of KL-6 [29] and hydrogen peroxide in the blood of patients with interstitial pneumonia and COPD [30]. At the same time, we confirmed whether platinum-palladium activates AMPK at the in vivo and in vitro levels.

2. Materials and Methods, Cases

2.1. Case Patient

- 89-year-old male.
- Height 172 cm, weight 68 kg, body surface area 1,800 m2.
- Smoking history: None.
- Diagnosis: Interstitial pneumonia.
- Age at onset of interstitial pneumonia: 85 years old (as of 2020)
- Underlying diseases: None.
- Platinum-palladium intake: 18 ml/day (6 ml/1 vial x 3 vials).
- Duration: 32 months.
- Drug treatment: None.
- Oxygen inhalation: None.

2.2. History

In daily life, the patient walked 2-3 km every day to maintain and improve his health. No history of smoking, but alcohol consumption. Suddenly, frequent coughing was confirmed, and although cough suppressants were prescribed, there was no sign of improvement. When the patient was re-examined at a city hospital, chest X-rays and other tests confirmed findings specific to interstitial pneumonia, and he was diagnosed with interstitial pneumonia. The patient was told by his doctor

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that he had only two years to live. The disease gradually progressed, and he had difficulty breathing even when doing everyday activities such as climbing the stairs or going to the toilet at home, and he would often collapse. He lost the will to move, but by taking platinum-palladium, his respiratory function improved on the 18th day, his coughing almost disappeared, and her breathing difficulties decreased. At the time of his final visit, he had improved enough to resume walking. However, during the period when he stopped taking platinum-palladium, he experienced breathing difficulties again.

3. Measurements at *In Vitro* and *In Vivo* Levels

3.1. AMPK Measurement

Study of AMPK activity by platinum-palladium

In this experiment, we used the Cyclex® AMPK Kinase Assay Kit (MEDICAL & BIOLOGICAL LABORATORIES CO., LTD. Tokyo, Japan) as per the usual method, and compared AMPK activity in the platinum-palladium-added group (final concentration 1%) with the PBS-added group as a control, using a purchased human breast cancer cell line (MCF-7). In this kit, the current activity of AMPK was measured 1 hour, 12 hours, and 24 hours after addition. The evaluation was performed using statistical software (IBM SPSS Statistics Ver.26) with the Mann–Whitney U test.

3.2. Measurement of Blood KL-6

Study of KL-6 fluctuations due to platinum-palladium

The study included 16 subjects (hereafter referred to as subjects) who visited Hino Kosei Clinic and agreed to participate in the study. Each subject was administered platinum-palladium for 28 days (4 weeks). The dosage was 3 vials in the first week, 2 vials in the second week, and 1 vial in the last 2 weeks. KL-6 was measured before and after administration and compared. The evaluation was performed using statistical software (IBM SPSS Statistics Ver.26) with the paired t-test.

KL-6 was measured by enzyme immunoassay (EIA) as per the standard method, with a standard value of less than 500 U/mL [31,32].

3.3. Measurement of Blood hydrogen Peroxide (Figure 3.)

Study of changes in hydrogen peroxide due to platinum-palladium

The study included 12 subjects (hereafter referred to as subjects) who visited Hino Kosei Clinic and agreed to participate in the study. Each subject was given platinum-palladium for 28 days (4 weeks). The subjects were given 3 vials in the first week, 2 vials in the second week, and 1 vial in the last 2 weeks. Hydrogen peroxide was measured before and after administration and compared. In addition, the results were statistically evaluated using a paired t-test with statistical processing software (IBM SPSS Statistics Ver.26).

Qualitative measurement of hydrogen peroxide was performed using the peroxidase-diaminobenzidine method.

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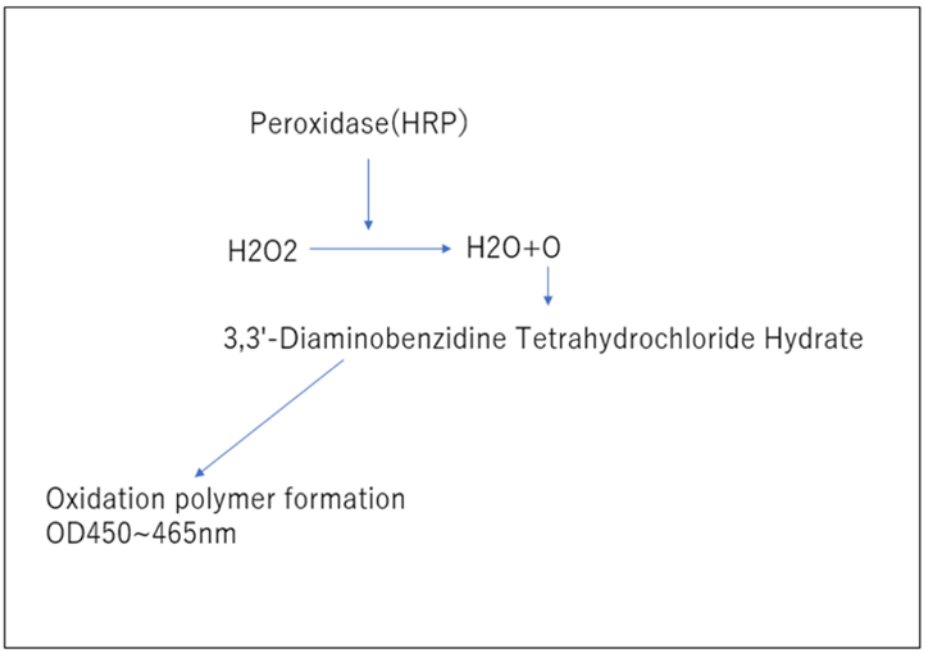

Figure 3. Hydrogen peroxide measurement principle.

3.4. Study on the Effect Of Platinum-Palladium on Symptom Improvement in Patients With Interstitial Pneumonia

32 patients with interstitial pneumonia were given platinum-palladium for one to three months, 3 vials for the first week, 2 vials for the second week, and 1 vial for the last two weeks, and clinical judgment was made. In this study, the subjects were patients with KL-6>500U/mL, crepitus+ in breath sounds, and + in X-ray reading.

4. Results

4.1. AMPK Measurement

When platinum-palladium was administered to MCF-7 and AMPK activity was measured, it was confirmed that the activity increased significantly in all groups at a significance level of 1% when the control group was taken as 100%. (Table1. 2, Figure 4.)

Table 1. Absorbance of control and platinum-palladium-added groups.

(1) Absorbance

1hr		**12hrs**		**24hrs**	
Cnt	Pt:Pd	Cnt	Pt:Pd	Cnt	Pt:Pd
0.285 ± 0.013	2.308 ± 0.223	0.352 ± 0.019	2.689 ± 0.447	0.264 ± 0.034	2.341 ± 0.082

Table2. AMPK activity when compared to the control group (100%).

(2) AMPK activity

1hr		**12hrs**		**24hrs**	
Cnt	Pt:Pd	Cnt	Pt:Pd	Cnt	Pt:Pd
100%	809.80%	100%	763.92%	100%	886.74%

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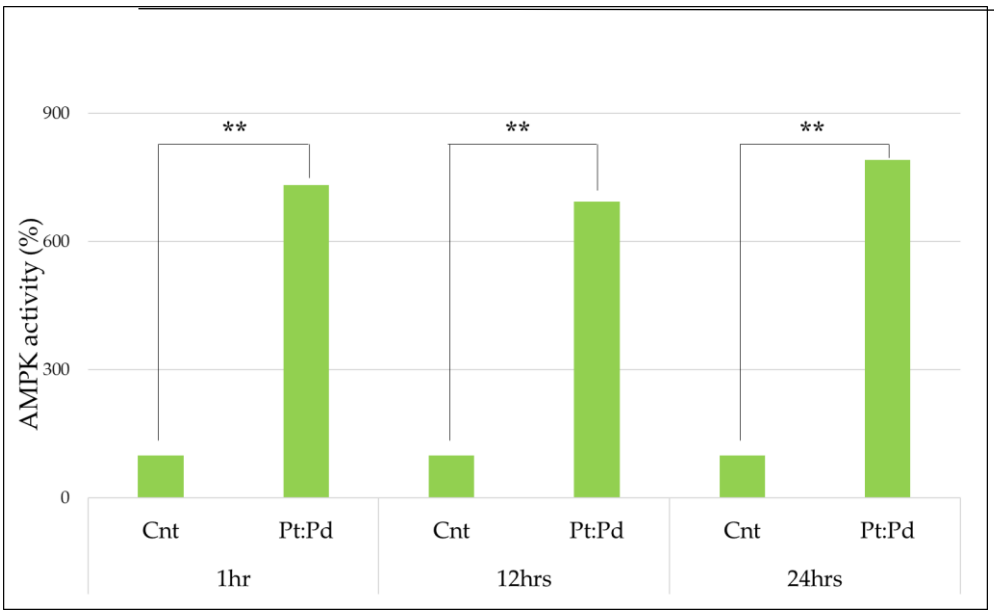

Figure 4. AMPK activity in platinum-palladium compared to the control group (100%) (Mann-Whitney U test. P<0.01).

4.2. Measurement of Blood KL-6

In n=16 subjects, a tendency for the KL-6 value to decrease was observed as shown in Table 3 and Figure 5 below. Furthermore, statistical processing revealed a significant decrease at a significance level of 5%. This suggests that the escape of KL-6 from the alveoli is suppressed, suggesting the possibility of improved alveolar function.

(Table 3, Figure 5)

Table 3. Comparison of KL-6 before and after administration of platinum-palladium (n=16).

KL-6 (IU/ml)

Case	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩	⑪	⑫	⑬	⑭	⑮	⑯
Before	583	276	509	253	679	268	321	224	726	137	103	674	168	787	752	89
After	351	203	367	272	474	315	298	205	622	171	189	422	193	525	473	91

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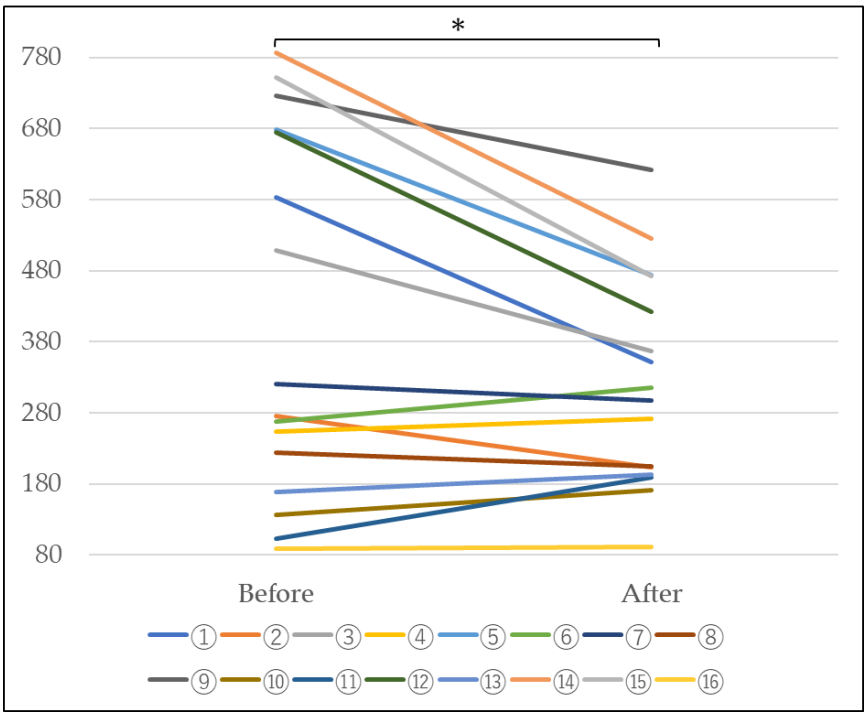

Figure 5. Changes in KL-6 before and after platinum-palladium administration（Paired-samples t-test. P<0.05）.

4.3. Measurement of Blood Hydrogen Peroxide

When blood hydrogen peroxide levels were measured in n=12 subjects, a de- crease was observed at a significance level of 5%, as shown in Table 4 and Figure 6 Since there is thought to be a relationship between interstitial pneumonia and hydrogen peroxide, these results suggest that interstitial pneumonia caused by hydrogen peroxide may improve.

(Table 4, Figure 6.)

Table 4. Changes in blood hydrogen peroxide levels due to platinum-palladium（U）.

Case	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩	⑪	⑫
before	284	243	368	311	307	267	363	307	311	240	289	297
after	250	224	282	212	314	206	247	274	279	206	295	283

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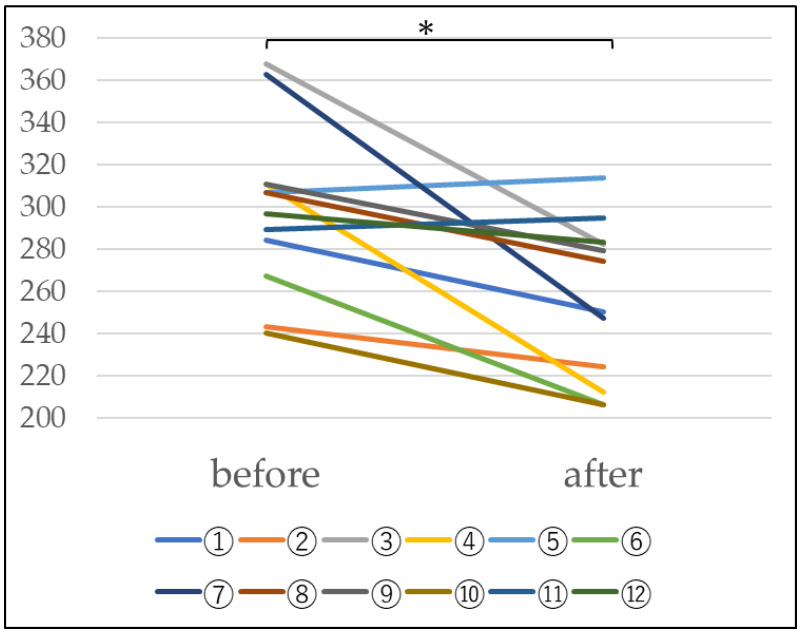

Figure 6. Changes in blood hydrogen peroxide levels before and after administration of platinum-palladium（Paired-samples t-test. P<0.05）.

4.4. Investigation Into The Effectiveness Of Platinum-Palladium In Improving Symptoms In Patients With Interstitial Pneumonia (Figure 7.)

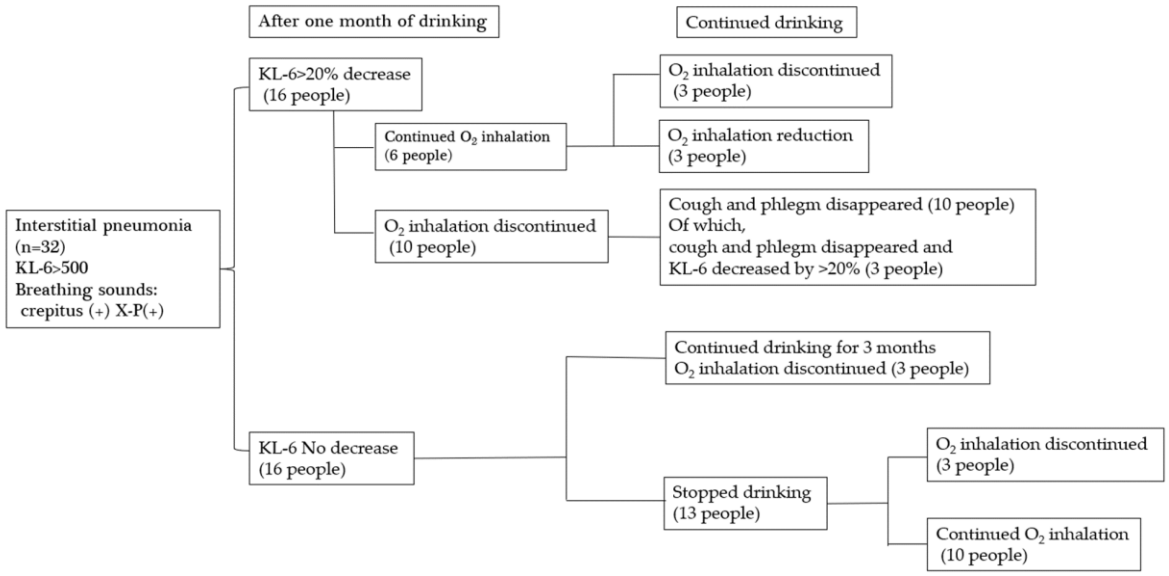

Figure 7. Changes after drinking platinum-palladium.

Thirty-two patients with interstitial pneumonia who visited Hino Kosei Clinic and Kisaragi Soken Clinic took platinum-palladium and their progress was monitored. Sixteen of the 32 patients showed a 20% or greater decrease in KL-6 after one month. Ten of them stopped inhaling oxygen after one month, and all ten patients also stopped coughing and sputum. Three of them showed a further 20% decrease in KL-6. Six patients continued to take oxygen after one month, even though their KL-6 had decreased by more than 20%, but three of them stopped taking oxygen and three had their dose reduced after continued intake. This suggests the need to continue taking platinum-palladium . Sixteen of the 32 patients showed no decrease in KL-6 after one month, but they were

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able to stop taking oxygen after three more months of continued intake. Of the patients who stopped drinking the water after one month, three subsequently stopped oxygen inhalation and 10 continued oxygen inhalation; however, this does not mean that the platinum-palladium was ineffective, but rather that the patients discontinued drinking it due to unavoidable circumstances. Therefore, it is possible that their condition would have improved if they had continued drinking it.

4. Discussion

This is a case report in which platinum-palladium improved the pathology of interstitial pneumonia. In addition to this case, there have been many reports of improvement in other clinics, and many cases of improvement in interstitial pneumonia with platinum-palladium have been confirmed. Therefore, it was suggested that platinum-palladium is an effective treatment method for interstitial pneumonia. Currently, treatment for interstitial pneumonia is mainly conservative, with the aim of preventing the condition from worsening, but improvement is difficult. However, in this case, improvement in daily living activities was observed, so it is possible that lung function may have improved. Although there are still many unknown aspects of the mechanism, we have considered the possibility. Although the cause of interstitial pneumonia is often unknown, it causes inflammation in the interstitium, so the production of reactive oxygen species is thought to be the cause [33]. Reactive oxygen releases inflammatory cytokines and has a positive aspect as a system to defend the body, but excessive reactive oxygen is known to have a negative effect on normal cells, causing lifestyle-related diseases, aging, and chronic inflammation [34,35]. In this case, platinum-palladium was used, but as mentioned above, platinum-palladium causes moderate antioxidant activity, so it is possible that it did not remove necessary reactive oxygen, but only unnecessary reactive oxygen, which may have led to the improvement of interstitial pneumonia. In addition, when the activity of AMPK by platinum-palladium was confirmed at the in vitro level, AMPK activity was confirmed at a significance level of 1% in all groups. AMPK (AMP-activated protein kinase) is an energy sensor in the body and is a serine/threonine kinase that works to maintain homeostasis of glucose and lipid metabolism [36]. It is said that activation of AMPK regulates energy metabolism and maintains energy homeostasis, and it has attracted attention as a potential therapeutic agent for metabolic diseases including type 2 diabetes and cancer [36]. Energy is essential for human life, and the source of energy is ATP (adenosine triphosphate), which is generated when ATP is hydrolyzed and converted into ADP (adenosine diphosphate) [37]. AMPK regulates ATP levels to maintain homeostasis and is expected to be effective against metabolic diseases such as cancer, type 2 diabetes, and obesity [38,39,40]. It is thought that AMPK regulates metabolism by inhibiting ATP consumption pathways [41,42]. Therefore, AMPK contributes to maintaining health in the body by suppressing chronic inflammation [43,44]. It promotes autophagy [45]. It may increase mitochondrial function [46] and increase intracellular ATP levels by activating mitochondrial biosynthesis [47,48].

In other words, it is thought that increasing AMPK activity can prevent lifestyle-related diseases, including cancer. It is thought that AMPK regulates metabolism by inhibiting ATP consumption pathways. There are reports that AMPK activity reduces abnormal inflammatory responses and cellular aging, leading to the treatment of interstitial pneumonia [49], and it was suggested that this effect could be used to play a role in improving interstitial pneumonia caused by platinum-palladium.

In addition, blood tests were performed on patients at the in vivo level to meas- ure the aforementioned KL-6 and blood hydrogen peroxide levels. KL-6 is a high molecular weight sialylated glycoprotein contained mainly in type II alveolar epithelial cells that is strongly involved in the production and secretion of pulmonary surfactant [50], and is widely used clinically to assess the severity of chronic respiratory diseases because it correlates with the activity (severity) of chronic respiratory diseases [51], and is released into the blood due to inflammatory damage to the alveoli [52,53]. It is strongly correlated with the severity of interstitial pneumonia, but it has also been reported to correlate with the severity of lung cancer and mixed disorders (combined with emphysema) [54], and is used clinically [55].In this experiment, the KL-6 value was significantly reduced, suggesting that the severity had improved. In the future, we plan to investigate what action in the body's dynamics is suppressing the release of KL-6, but one hypothesis is that this is due to

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improved alveolar function in patients with interstitial pneumonia. At the same time, hydrogen peroxide (H_2O_2) was examined. Hydrogen peroxide (H_2O_2) is one of the representative reactive oxygen species (ROS) [56], and in normal physiological actions, it plays an important role in cell signaling, etc. [57], but on the other hand, it induces oxidative stress in the body and is a factor in cell and tissue damage [58,59]. When glucose is ingested in the body, it enters the TCA cycle through the glycolysis process and then passes through the electron transport system to produce ATP [60], but when glucose cannot be ingested, fat and protein are burned to produce ATP. In other words, ATP is essential for human life support [61]. A large amount of oxygen is required to produce this ATP, and naturally this oxygen is taken in through breathing. Most of it is involved in energy production, but a few percent of it is converted into reactive oxygen species (ROS) [62]. ROS have advantages and disadvantages for the body. One advantage is that ROS play a role in the body's defense mechanism, destroying bacteria and cancer cells in granules contained in neutrophils [63]. It is known that ROS are related to various lifestyle-related diseases, including malignant neoplasms, and aging [64]. Currently, the following four types of ROS are known to exist: 1) Superoxide (O2-), 2) Hydrogen peroxide (H_2O_2), 3) Hydroxyl radical (·OH), and 4) Singlet oxygen ($_1O_2$) [65]. In recent years, methods for removing ROS have been studied both in Japan and overseas for the purpose of preventing diseases and combating aging [66]. Since aging has been treated as a disease name since ICD-11, [67]it is expected that further research on antioxidants will be conducted in the future. In this context, it has been confirmed that platinum-palladium is the only substance in the world that can remove all four types of reactive oxygen mentioned above [68]. In this study, from the perspective that there may be a possibility that hydrogen peroxide is generated in large amounts in patients with interstitial pneumonia before and after taking platinum-palladium, [69] the plasma hydrogen peroxide level was qualitatively measured, and a significant difference was observed in this experiment, confirming a tendency for hydrogen peroxide to decrease in the body when platinum-palladium was used. Hydrogen peroxide is a type of reactive oxygen species [70], and it is possible that hydrogen peroxide may affect the alveoli in patients with interstitial pneumonia and COPD [71] Therefore, the fact that a decreasing trend was observed in this study indicates that platinum-palladium significantly reduced KL-6 and hydrogen peroxide in patients with interstitial pneumonia. This suggests that platinum-palladium may be effective at the pharmaceutical level not only for interstitial pneumonia but also for COPD by protecting the alveoli in the reduction of KL-6, suppressing the effects of ROS caused by hydrogen peroxide, and increasing mitochondrial activity.

5. Ethical Considerations

This study was conducted with the approval of the Hino Kosei Clinic Ethics Comittee. Ethics Review Numbers HKC_N10023001, HKC_N10023002, HKC_N10023003, HKC_N10023004)

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