Journal of Pigmentary Disorders
ISSN: 2376-0427

Shibata et al., Pigmentary Disorders 2015, 2:6
DOI: 10.4172/2376-0427.1000184

Research Article Open Access

The Novel Therapy for Vitiligo Vulgaris: Topical Use of Cosmetic Cream of Platinum Nanoparticles and Palladium Nanoparticles which Show Strong Catalase-like Activity

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Abstract

Background: Vitiligo is an acquired skin disease characterized by loss of melanin pigment due to disappearance of functional melanocytes. Several treatments are recommended worldwide, but none is really effective. Topical use of materials having high catalase activity is suggested to be effective to regain melanin pigment in the vitiligo skin.

Objective: To investigate the efficacy and safety of topical use of PAPLAL which has extremely high activity of catalase in the treatment of vitiligo vulgaris subjects.

Methods and Patients: 58 patients with vitiligo vulgaris who suffered more than 10% skin area and were refractory to the conventional therapies during the last one year or more. PAPLAL cream containing platinum (Pt, 139 μM) and palladium (Pd, 40 μM) nanoparticles, or PAPLAL lotion (Pt:5 μM, Pd:7 μM) was topically applied two times a day at the depigmented skin, mainly face and the back side of the hands and fingers which are well recognized as the sites resistant to the common therapies, or PAPLAL water (PT:1.03 mM, Pd:2.82 mM) was orally administered once a day. Therapeutic efficacy was evaluated by a dermatologist when the patients visited to the clinic mostly at every two weeks or every one month.

Repigmentation effect was evaluated using photographs taken before and after the treatments of the selected vitiligo areas, face, the back of the hands or trunk by a single dermatologist. The treatment response was evaluated as follows; excellent: more than 50%, good: >10%, <50%, moderate: >5%, <10%, poor to none: less than 5%. We regarded the cases responded more than 10% repigmentaton after PAPLAL treatment as effective. The time points of evaluation were not fixed, but carried out at 2, 4, 8 weeks, and 3, 6 and 12 months after the initiation of the treatment.

Results: PAPLAL cream was the most effective, as 58% patients had more than 10% repigmentation, compared to 35.2% and 11.1% of PAPLAL lotion and water, respectively. Two patients treated with PAPLAL cream exhibited erythema around 8 weeks after the intiation of the treatment.

Conclusions: Our results have shown that PAPLAL cream and lotion may be the effective topical agents to treat vitiligo patients, since it showed a high efficacy of repigmentation of vitiligo cases who had not responded to the conventional modalities including excimer radiation therapy.

Keywords: Vitiligo; PAPLAL; Palladium; Platinum nanoparticles

Abbreviations: Pt: Platinum; Pd: Palladium; ROS: Reactive Oxygen Species; CRT: Calreticulin; Tsh: Topical steroid hormone; Tv3: Topical vitamin D3; Excim: Excimer Lamp; IPD: Suplatact tosilate; PAPC: PAPLAL cream; PAPL: PAPLAL lotion; PAPw: PAPLAL water

Introduction

Vitiligo is an acquired depigmenting disorder characterized by loss of melanin pigment from epidermis due to disappearance of functional melanocytes. The prevalence of the disease is around 1% worldwide [1-3]. The underlying mechanisms of vitiligo, however, still remains to be clarified, but autoimmune related factors [4-7] and oxidative stress [8-10] are proposed to be the most probable causes of the disease. The clinical observation that vitiligo is occasionally associated with other autoimmune diseases, suggests an immunological pathological role in vitiligo [5,6,7,11]. Further, there are a number of studies in support of cell-mediated auto-immune in vitiligo. Owing to the location, melanocytes are vulnerable to exogenous chemical physical and their metabolites which produce reactive oxygen species (ROS), particularly H_2O_2 [12]. In the epidermis and to a lesser extent the vascular organ of active vitiligo patients have been reported to be affected by the high level of H_2O_2, in association with a lower expression and lower activity of the antioxidant enzyme catalase [9,13], although whether H_2O_2 is the primary cause or the consequence needs to be studied. Excess production of H_2O_2 may induce apoptosis in melanocytes, leading to the development of vitiligo caused by the disappearance of melanocytes from epidermis [14]. Melanocytes serve as ROS scavengers and further, reported to play a role in the skin immunity by secreting a wide range of signal molecules and cytokines relevant to immune system [15].

Recently, H_2O_2 stress-induced calreticulin (CRT) has been shown to play a significant role of melanocyte destruction by apoptosis and suggested a relationship between apoptosis and immune reactions in melanocyte killing [16]. Further, when melanocytes are under H_2O_2-mediated oxidative stress, CRT translocates to the cell surface, increasing melanocyte immunogenicity and serving as a key step linking

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Received April 29, 2015; **Accepted** May 10, 2015; **Published** May 25, 2015

Citation: Shibata T, Yoshikawa R, Ichihashi M (2015) The Novel Therapy for Vitiligo Vulgaris: Topical Use of Cosmetic Cream of Platinum Nanoparticles and Palladium Nanoparticles which Show Strong Catalase-like Activity. Pigmentary Disorders 2: 184. doi:10.4172/2376-0427.1000184

apoptosis and the immune reactions that may provide a paradigm for melanocyte apoptosis. These results indicate the importance of ROS in the development of vitiligo, owing to the destruction of melanocytes even by the immune reactions.

Based on these reports, we speculated that a strong anti-oxidant, platinum nanoparticles added with palladium which protects platinum against oxidative deterioration quite efficiently, without toxic adverse effect on human skin cells, may recover epidermal melanocyte function in vitiligo patients and regain constitutive melanin in epidermis [17]. 58 subjects suffering from vitiligo vulgaris at the average duration of 14.8 years and had not responded to the treatments by conventional therapies were enrolled in our study. The clinical study began on January 6, 2014. 10 patients were treated with oral intake of PAPLAL once a day till 4 months which contains platinum (Pt) at the dose of 0.6 mg/3 ml + palladium (Pd) at the dose of 0.9 mg/3 ml water kept in the amples for medical use. 17 patients were treated with topical application of the PAPLAL lotion and 31 cases were treated with PAPLAL cream which are used for cosmetics. We found that 7 out of 31 vitiligo patients responded extremely well to the PAPLAL cream treatment, and partial and almost complete recovery of melanin pigmentation at the depigmented skin area, in 5 and 2 patients, respectively. During the last one year study period, we finally found 58.1% (18/31) partial and complete repigmentation by topical application combined with excimer light. During PAPLAL application, patients were not treated with other drugs.

We propose that the topical use of platinum nanoparticles with palladium is one of the promising therapies for long lasting and even rebellant vitiligo cases.

Patients and Methods

Materials

PAPLAL, a product containing platinum (Pt) and palladium (Pd) as nanoparticles, was supplied by Musasino Pharmaceutical Co. Tokyo, Japan. PAPLAL is composed of a mixture of 0.2 mg/ml (1.03 mM) of Pt and 0.3 mg/ml (2.82 mM) of Pd nanoparticles.

Three kinds of PAPLAL products were used in this study:

1. Three ml of PAPLAL water (Pt and Pd nanoparticle) in an ample containing Pt and PD at the concentration of 1.03 mM and 2.82 mM respectively was orally taken once a day during fasting time for at least three months in 15 patients.

2. PAPLAL lotion containing Pt and Pd at the concentration of 0.023 mM and 0.067 mM respectively was applied to the skin twice a day for 3 to 6 months.

3. PAPLAL cream containing Pt and Pd at the concentration of 0.139 mM and 0.376 mM respectively was topically applied to the depigmented skin twice a day for 3 to 12 months.

Patients

The 58 patients with the clinical subtype vitiligo vulgaris (19 males and 39 female) a mean age of 38.8 years (range: 2-74 years) who did not responded to the conventional therapies were included in this study. The mean duration of the disease was 14.9 years (range: 9 months-50 years). The treatments prior to our present study which patients received were narrow band UVB, excimer light, topical corticosteroids, topical vitamin D, and topical application of tacrolimus ointment for at least more than one year except two cases {a 8-year-old girl treated for 9 months (case 31) and a 7-year-old boy treated for 11 months (case 17)}, were not effective in the induction of repigmentation in the lesional skin, even by combination of these modalities, and in some patients, spreading of the depigmented areas during and after the treatments observed.

Further, the vitiligo vulgaris patients were enrolled to the present study based on the following criteria : (1) less than 30% involvement of the body surface area, (2) more than one year since the onset of the disease. The patients with pregnancy and/or duration hyper-photosensitivity were excluded.

Blood examination to detect autoimmunity related diseases, such as rheumatoid arthritis, lupus erythematosus and thyroid diseases was performed in the patients who had any symptom and sigh of autoimmunity. Informed consent was obtained from all patients, and the study was approved by the local ethics institutional board.

Results

58 Japanese patients comprising 39 female and 19 male with vitiligo vulgaris who did not respond to the conventional treatment modalities including excimer light therapy for more than one year were enrolled in the present clinical study. Two patients failed to continue the PAPLAL cream treatment for more than 3 months, due to itchy erythema developed on the treated skin on the 8th week of the treatment were included in the analytical study. No side effect was found in the group treated with PAPLAL lotion, but in PAPLAL water group, one male 74-year-old patient felt ill immediately after drinking an ample of PAPLAL water. We could not examine the cause of his illness, since he denied any tests we proposed. Further, the patient did not visit the doctor again, he was excluded from the analysis. The average duration of the disease of the 3 treatment groups was 14.4 ± 11.9 years. Extent of the disease area was less than 20% in nearly 70% of the enrolled cases. Clinical characteristics and previous treatments of the patients received before the present trial were summarized in Table 1.

All the patients continued to be treated with excimer light in addition to PAPLAL-cream, -lotion or -water. Since we aimed to treat the enrolled patients without any anxiety for the novel treatment using PAPLAL which has not been used for vitiligo treatments previously, we agreed with the patients request to continue excimer light therapy in addition to PAPLAL.

PAPLAL cream was the most effective among three treatment categories, possibly due to the highest concentration of Pt and Pd in the cream. In PAPLAL cream group, 58% patients had more than 10% repigmentation in vitiligo, while PAPLAL lotion- or PAPLAL water-treated patients showed the efficacy over 10% repigmentation was 35.2 % and 11.1% of respectively (Table 2). Two patients treated with PAPLAL cream exhibited erythem reaction on day 7 in one case and at 5 months later in the other case. The first case was excluded, but the later case was included in the analytical study.

Three cases of significant repigmentation in depigmented skin after treatment with PAPLAL cream + excimer light for one month, three months, and 6 months were shown in Figures 1, 2 and 3, respectively.

Palladium is widely used in dentistry and in the production of jewellery and watches, and recent epidemiological data suggest that the prevalence of palladium allergy is around 7% in dermatitis and dental patients. To see a possibility of allergic reaction in patients who have been diagnosed to have allergy to palladium and other metals, PAPLAL cream and lotion were painted at the inner sides of right and left upper arms respectively and observed the skin reaction for a week (Table 3). 8 patients did not show any allergic cutaneous response, but one patient

Case Number	Age	Sex (M,F)	Onset of vitiligo (age)	Disease duration (ys)	Past Treatments	Present treatments	Beginning of PAPC (y/m/d)	Repigmentation effects of PAPC
1	27	F	2	25	Tsh, Tv3, IPD, Excim	PAPC, Excim	1/14/2014	Excellent
2	34	M	26	8	Tsh, Tv3, IPD, Excim	PAPC, Excim	5/12/2014	Excellent
3	57	M	27	30	Tsh, Tv3, IPD, Excim	PAPC, Excim	12/20/2013	None
4	42	M	32	10	Tsh, Tv3, IPD, Excim	PAPC, Excim	1/14/2014	Good
5	74	M	61	13	Tsh, Tv3, IPD, Excim	PAPC, Excim	1/10/2014	Excruded due to side effect
6	54	F	34	20	Tsh, Tv3, IPD, Excim	PAPC, Excim	1/10/2014	Good
7	43	M	13	30	Tsh, Tv3, IPD, Excim	PAPC, Excim	12/19/2013	Excellent
8	63	F	58	5	Tsh, Tv3, IPD, Excim	PAPC, Excim	1/16/2014	Good
9	72	F	70	2	Tsh, Tv3, IPD, Excim	PAPC, Excim	12/27/2013	Good
10	50	M	47	3	Tsh, Tv3, IPD, Excim	PAPC, Excim	3/20/2014	None
11	35	M	11	25	Tsh, Tv3, IPD, Excim	PAPC, Excim	5/17/2014	Excruded due to side effect
12	43	F	31	12	Tsh, Tv3, IPD, Excim, PAPw	PAPC, Excim	5/17/2014	Moderate
13	36	F	32	4	Tsh, Tv3, IPD, Excim, PAPw	PAPC, Excim	6/6/2014	Good
14	40	F	10	30	Tsh, Tv3, IPD, Excim, PAPw	PAPC, Excim	3/15/2014	Good
15	65	F	23	42	Tsh, Tv3, IPD, Excim, PAPw	PAPC, Excim	6/15/2014	Moderate
16	49	F	37	12	Tsh, Tv3, IPD, Excim	PAPC, Excim	7/11/2014	Moderate
17	8	F	8	11m	Excim	PAPC, Excim	7/5/2014	None
18	40	F	24	16	Tacr, Tv3, IPD, Excim, PAPw	PAPC, Excim	7/8/2014	Excellent
19	70	F	64	6	Tacr, Tv3, IPD, Excim, PAPw	PAPC, Excim	7/24/2014	Excellent
20	39	F	28	11	Tsh, Tv3, NB-UVB	PAPC, Excim	7/24/2014	None
21	20	F	5	15	Tsh, Tv3, IPD, VTRAC	PAPC, Excim	7/26/2014	Good
22	7	F	3	4	Tsh, Tv3, IPD, VTRAC	PAPC, Excim	7/26/2014	None
23	6	F	3	3	Tv3, Excim,	PAPC, Excim	7/26/2014	Moderate
24	2	F	1	1	Tsh, Excim	PAPC, Excim	8/1/2014	Good
25	4	F	2	2	Tsh, Tv3, IPD, Excim	PAPC, Excim	8/4/2014	Good
26	42	F	18	24	Tsh, Tv3, IPD, Excim	PAPC, Excim	8/8/2014	Excellent
27	5	M	2	3	Tsh, Tv3, Excim, PAPw	PAPC, Excim	8/26/2014	Excellent
28	41	F	19	22	Tv3, VTRAC	PAPC, Excim	9/12/2014	moderate
29	31	F	12	19	Tsh, Tv3, IPD, Excim	PAPC, Excim	9/18/2014	None
30	31	F	11	20	Tv3, Excim,	PAPC, Excim	9/17/2014	Good
31	7	M	2	9m	Tsh, Tv3	PAPC, Excim	12/25/2014	Good, eyebrow pigmented
32	9	F	4	5	Tsh, Tv3, IPD, Excim	PAPL, Excim	12/20/2013	None
33	9	F	2	7	Tsh, Tv3, IPD, Excim	PAPL, Excim	12/21/2013	Moderate
34	8	F	3	5	Tsh, Tv3, IPD, Excim	PAPL, Excim	12/21/2013	Good
35	34	M	29	5	Tsh, Tv3, IPD, Excim	PAPL, Excim	12/21/2013	Good
36	39	M	30	9	Tsh, Tv3, IPD, Excim	PAPL, Excim	12/24/2013	None
37	38	M	30	8	Tsh, Tv3, IPD, Excim	PAPL, Excim	12/24/2013	None
38	45	M	15	30	Tsh, Tv3, IPD, Excim	PAPL, Excim	12/24/2013	moderate
39	56	M	47	9	Tsh, Tv3, IPD, Excim	PAPL, Excim	12/26/2013	None
40	40	F	23	17	Tsh, Tv3, IPD, Excim	PAPL, Excim	1/17/2014	Good
41	64	F	52	12	Tsh, Tv3, IPD, Excim, PAPw	PAPL, Excim	2/7/2014	Good
42	7	F	3	4	Tsh, Tv3, IPD, Excim, PAPw	PAPL, Excim	12/20/2013	None
43	51	F	46	5	Tsh, Tv3, IPD, Excim, PAPw	PAPL, Excim	12/21/2013	Moderate
44	51	F	1	50	Tsh, Tv3, IPD, Excim, PAPw	PAPL, Excim	12/21/2013	Good
45	53	F	38	15	Tsh, Tv3, IPD, Excim, PAPw	PAPL, Excim	12/21/2013	Good
46	72	M	64	8	Xcim, Tacr	PAPL, Excim	12/24/2013	None
47	15	F	10	5	Xcim, Tacr, IPD	PAPL, Excim	12/24/2014	None
48	7	F	2	5	Xcim, Tacr, IPD	PAPL, Excim	12/24/2014	Moderate
49	36	F	30	6	Tsh, Tv3, IPD, Excim	PAPW, Excim	12/18/2013	Good
50	65	F	29	36	Tsh, Tv3, IPD, Excim	PAPW, Excim	12/15/2013	None
51	43	F	31	12	Tsh, Tv3, IPD, Excim	PAPW, Excim	12/24/2013	Moderate
52	49	M	12	37	Tsh, Tv3, IPD, Excim	PAPW, Excim	1/16/2014	Moderate
53	50	M	47	3	Tsh, Tv3, IPD, Excim	PAPW, Excim	12/20/2013	None
54	64	F	52	12	Tsh, Tv3, IPD, Excim	PAPW, Excim	12/27/2013	Moderate
55	34	M	9	25	Tsh, Tv3, IPD, Excim	PAPW, Excim	12/28/2013	None
56	62	F	26	36	Tsh, Tv3, IPD, Excim	PAPW, Excim	1/4/2014	None
57	40	F	10	30	Tsh, Tv3, IPD, Excim	PAPW, Excim	12/20/2013	None
	38.2 ± 20.7		23.9 ± 19.3	14.8 ± 11.9				

Table 1: PAPLAL 57 cases.

Response categories	Response rate % (No. of cases) of Treatment group PAPLAL + Ecximer		
	Cream	Lotion	Water
Excellent	22.6 (7)	0 (0)	0 (0)
Good	35.5 (11)	35.3 (6)	10 (1)
Moderate	16.1(5)	29.4 (4)	30 (3)
Poor and None	19.4 (6)	41.2 (7)	50 (5)
Side effects	6.5 (2)*	0 (0)	1**
Excellent + Good	**58.1**	**35.3**	**10**
E + G + M	77.5	64.7	40
	* : itchy erythema		
	** :ceasation of treatment		

Table 2: PAPLAL.

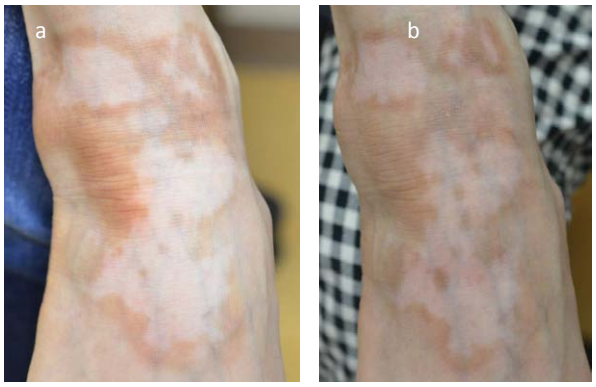

Figure 1: 25-year-lasting-hypopigmented lesions on the back of the right foot joint of 36-year-old female patient. The patient received excimer light treatment more than one year before the initiation of PAPLAL cream topical application. Before (a) and after treatment with PAPLAL cream (b). Increase of the size of pigmented spots within depigmented skin and darker pigmentation at the marginal areas were observed after one month treatments.

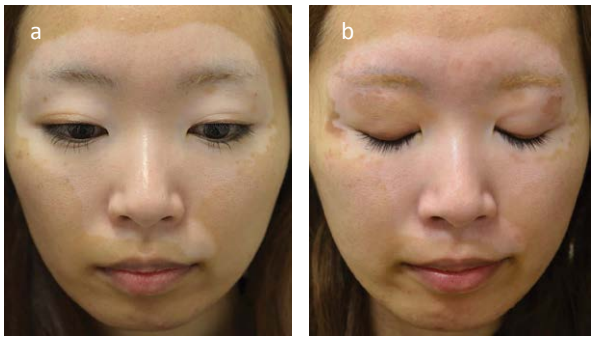

Figure 2: 27-year-old female suffering from depigmented macules on her face for around 25 years. Pigmentation status before (a) and 9 months-treatment with PAPLAL cream (b).

showed a few normal colored tiny papules indicating mild irritant reaction in the test skin site at 48 h and 7 days after PAPLAL cream application, suggesting a low possibility of PAPLAL cream and lotion to be an allergic substance compared with palladium chloride.

Discussion

The present study was aimed to evaluate the repigmentation efficacy of PAPLAL which contains platinum (Pt) and palladium (Pd) functioning as antioxidant of their strong catalytic activity in nanocolloidr, on vitiligo vulgaris skin. We enrolled vitiligo vulgaris patients who had not responded to the single and combination of various conventional modalities, such as excimer light, narrowband UVB light, PUVA, topical use of steroids, vitamin D and tacrolims for at least one year treatments [18-21]. We surprisingly found that topical application of the cream containing 0.14 mM Pt and 0.38 mM Pd was very effective to recover melanin pigment in vitiligo skin in 58.0% cases, compared to 38.2% of the lotion containing Pt and Pd at the concentration of 0.03 mM and 0.07 mM respectively. PAPLAL water applied orally was the least effective of 11.1% repigmentation among 9 cases.

Vitiligo vulgaris is an acquired depigmenting skin disoder affecting approximately 1% of the population worldwide [1]. The etiology of vitiligo vulgaris is not fully understood, although several hypotheses have been proposed for the loss of functioning melanocytes in the skin, including the genetic factors, cell-mediated, humoral and autoimmune responses, and oxidative stress [2,3,11,12,22]. The convergence theory suggests that oxidative stress, accumulation of toxic compounds, infection, autoimmunity, and apoptosis may contribute to vitiligo pathogenesis. In the early studies, cytotoxic T cells (CD8+ T cells) have been proposed to play a crucial role in vitiligo genesis by showing the presence of infiltrating CD8+ cells in generalized vitiligo by histochemical and immunohistochemical studies [6]. Recently, however, CD4+IL-17+Th17 cells are suggested to be important player in the induction of autoimmune vitiligo. Th17 cells produce IL-17 which upregulate TNFa, IL-6, and IL1-b, resulting in the inhibition of melanogenesis in melanocytes [5,23]. Recently, the role of oxidative stress-induced calreticulin translocated to the cell surface is proposed to play a role of melanocyte apoptosis which emits vital immunogenic signals and activate immune system [16]. In 2012, Toosi et al. suggested a role of unfolded protein response in melanocytes caused by oxidative stress which increases the production of IL-6 and IL-8, linking to environmental stresses and autoimmunity [24].

Conventional therapy for vitiligo includes topical corticosteroids and immunosuppressive ointments, and various kinds of phototherapies [18-21,25,26]. Based on the observation of low levels of catalase activity in both lesional and non-lesional skin of vitiligo patients, pseudocatalase, a bis-manganase -EDTA-(HCO3-)2 complex was used to treat vitiligo skin with remarkable repigmentation in 33 vitiligo patients [27]. Although another study [28] have failed to reproduce similar result, recently however, catalase/superoxide dismutase application was conducted to treat vitiligo skin and was found to be effective similar to topical corticosteroid therapy and had milder side effects compared to the corticosteroid treatment [29].

Based on these recent findings suggesting a pivotal role of ROS in

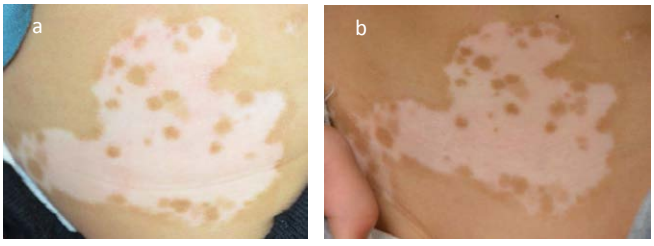

Figure 3: 34-year-male patient having depigmented skin on the trunk for 8 years. Increased repigmentation spots and macules within depigmented skin, and enhanced pigmentation at the marginal skin (b) were observed after two months treatment with PAPLAL cream in combination with excimer light. (a) is the status of depigmentation treated with excimer light.

Patient number	Age	Sex	Metals allergic to the patients	Response to PAPLAL cream and lotion used as is
1(MH)	23	F	nickel, palladium, gold	No
2(MO)	50	F	zinc, gold, palladium, platinum, copper	No
3(YO)	44	F	nickel, palladium	No
4(YT)	58	F	nickel, cobalt, palladium, platinum, chromium	a few number of normal coloured papules (cream)
5(HT)	50	F	zinc, nickel, copper, aluminum, chromium, palladium, iridium, iron, tin	No
6(AM)	64	F	platinum, zinc, manganese, palladium, tin	No
7(NY)	38	F	nickel, platinum, zinc, cobalt, chromium, palladium, tin	No
8(TY)	52	F	tin, chromium, gold, palladium, iron, cupper, ilidium, Inzume, mercury	No
9(KY)	69	F	unknown	No

Table 3: PAPLAL open skin application test.

the initiation and exacerbation of vitiligo vulgaris, we speculated that PAPLAL having a strong catalase activity converting H_2O_2 into water and oxygen molecule may effectively induce repigmentation of vitiligo skin by recovering normal niche required for melanocytes function to produce melanin pigment, if melanocytes in the depigmented skin are temporally inactive due to environmental factors, particularly ROS.

The efficiency of PAPLAL cream in the present study is rather high compared to other reports, even though we selected the patients for PAPLAL treatment solely from those who had not responded the various conventional vitiligo treatments. The lower efficacy of PAPLAL lotion could be its lower concentration of Pt and Pd compared to that of PAPLAL cream. PAPLAL water intake was found not to be so high to produce melanin in the vitiligo lesional skin, possibly due to the low concentration of Pt and Pd delivered to the lesional skin via blood stream after oral intake.

Pd is now considered to be one of the metals to cause contact allergy in contact dermatitis patients, and regarded as a clinical maker of nickel allergy [30-33]. Most of the patients with allergy to Pd are reported to have been exposed to Pd from jewellery and dental restorations. As in Japan, Pd is often used for dental patients, we tested the possibility of PAPLAL cream to act as an allergen to reproduce allergic response to the patients of a dental clinic who have been diagnosed to have allergy to Pd by skin patch test. 8 among 9 patients with Pd allergy did not show any inflammatory response to the use test with PAPLAL as is., suggesting a very low allergic ability of PAPLAL cream.

Two vitiligo cases in the present study who developed erythema in the PAPLAL cream-treated skin after around 8 weeks use, must be examined to have had Pd allergy, although the first case seems to be photo-allergic to the other drug which the patient began to take a few weeks before erythema developed in the combination therapy of PAPLAL and excimer light. Unfortunately, we could not carried out closed patch-test and photo-patch test to these two cases using Pd chloride and PAPLAL as is, but, it is important to confirm Pd allergy in our two cases for better understanding of allergic potentials of PAPLAL cream, if we try to open the way to use PAPLALs for the treatment of vitiligo patients in the near future.

This is the first report to show that topical use of Pt and Pd containing cream effectively produce repigmentation in the vitiligo skin after one to several months application in combination with excimer light treatment.

Judging from these results, we recommend PAPLAL cream as a novel and very much effective modality for the treatment of vitiligo vulgaris. However, further studies are necessary to confirm the efficacy of PAPLAL cream alone without other combination treatments, and to clarify the best concentration of Pt and Pd for vitiligo treatment, together with study to understand the basic mechanisms of PAPLAL to activate melanocytes for better application of PAPLAL to vitiligo vulgaris patients having different clinical subtypes and disease onset age and durations.

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