JDA Japanese Dermatological Association
THE JOURNAL OF DERMATOLOGY

doi: 10.1111/1346-8138.14634 *Journal of Dermatology* 2018; **45**: 1283–1288

ORIGINAL ARTICLE

Open-label pilot study to evaluate the effectiveness of topical bimatoprost on rhododendrol-induced refractory leukoderma

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ABSTRACT

Rhododendrol (RD), 4-(4-hydroxyphenyl)-2-butanol, inhibits melanin synthesis and had been used in skin-whitening cosmetic products until 2013. However, some individuals developed leukoderma on the skin where RD had been applied and have suffered from refractory depigmentation even after discontinuing RD application. Bimatoprost is a prostaglandin F2α analog and is often used for eyelash growth for cosmetic reasons as well as in the treatment of glaucoma. It was reported that bimatoprost induced skin pigmentation in addition to iris pigmentation as adverse effects. Therefore, we conducted an open-label single-center pilot study to evaluate the effectiveness of bimatoprost on refractory RD-induced leukoderma. Eleven Japanese female patients with skin type III who developed leukoderma on the exact or slightly extended area of skin where RD had been applied and gained a halt of enlargement of leukoderma or repigmentation on a part of the affected skin after discontinuation of RD were enrolled. Bimatoprost 0.03% solution was applied on the leukoderma once daily for 3 months, and then the frequency of application was increased to twice daily for the subsequent 3 months. Ten patients completed the 6-month course of bimatoprost application. In four patients, bimatoprost application brought slight improvement in RD-induced refractory leukoderma by dermatologists' evaluation. Because the number of enrolled patients was limited, further larger studies are necessary to better assess the effectiveness of bimatoprost in inducing repigmentation in patients with RD-induced refractory leukoderma.

Key words: **bimatoprost, depigmentation, leukoderma, melanocyte, rhododendrol.**

INTRODUCTION

Rhododendrol (RD), 4-(4-hydroxyphenyl)-2-butanol, inhibits melanin synthesis and had been used in skin-whitening cosmetic products until 2013. RD was effective in whitening skin. However, some individuals developed leukoderma on the skin where RD had been applied, and in some of them, leukoderma even extended to an area of skin where RD had not been applied.[1–3] Two percent of 800 000 users of RD cosmetic products complained of the development of leukoderma according to the manufacturer's report.[4] Most patients who developed RD-induced leukoderma obtained repigmentation in the affected skin by discontinuation of RD. However, some patients have suffered from refractory depigmentation even after discontinuing RD application.

Tanemura *et al.*[5] obtained skin biopsy samples from skin lesions in patients with RD-induced leukoderma. Histopathological examination revealed basal hypopigmentation, melanin incontinence and remaining melanocytes in most patients. Complete disappearance of melanocytes, relevant in vitiligo, was observed in a few patients. Several papers reported that RD exerts melanocyte toxicity in a tyrosinase-dependent manner, which leads to a reduction in melanin production.[2,6–9] Furthermore, damaged melanocytes induce the T-cell response and activation of melanocyte-specific cytotoxic lymphocytes, which may enhance depigmentation and possibly lead to the spread of depigmentation to non-exposed areas.[3,10]

Bimatoprost is a prostaglandin F2α analog and is often used for eyelash growth for cosmetic reason as well as in the treatment of glaucoma. It was reported that bimatoprost induced skin pigmentation and iris pigmentation as adverse effects.[11–15] Periocular pigmentation has been reported to occur more frequently with bimatoprost than with other prostaglandins.[14,16]

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Received 12 June 2018; accepted 2 August 2018.

Moreover, periocular pigmentation occurs more frequently in Asians than in Caucasians.[17–20] Increased frequency of periocular skin pigmentation has been reported with prolonged use of bimatoprost. Bimatoprost causes skin pigmentation by inducing an increase in melanosomes in dermal melanocytes.[21] Mediation of a prostaglandin-induced upregulation of tyrosinase is thought to be a possible mechanism of iris pigmentation caused by bimatoprost.[22] In one small study, bimatoprost was used to treat facial and non-facial vitiligo with moderate success,[12] although larger and long-term trials are pending.[16]

Therefore, we conducted an open-label single-center pilot study to evaluate the effectiveness of bimatoprost for the treatment of refractory RD-induced leukoderma.

METHODS

This was an open-label pilot study designed to examine the effectiveness and safety of bimatoprost for RD-induced leukoderma. Japanese patients visiting the Department of Dermatology of Teikyo University Hospital who developed leukoderma on the exact or slightly extended area of skin where RD had been applied and gained a halt of enlargement of leukoderma or gained repigmentation on a part of the affected skin after discontinuation of RD were recruited from July 2016 to December 2017. Patients who were suspected of having vitiligo were excluded. Eleven patients were enrolled in this study. In all 11 patients, the leukoderma on the neck or the hand had been refractory to previous treatments such as topical steroid or phototherapy for more than 2 years. The skin type of all patients was III. The patients were asked to apply bimatoprost 0.03% solution on the leukoderma on the left or right side once daily for 3 months, and then the frequency of application was increased to twice daily for the subsequent 3 months. In seven patients, RD-induced leukoderma on the contralateral side of the area treated with bimatoprost was not treated with bimatoprost as a control. One drop of bimatoprost 0.03% solution can be applied to approximately 50 cm^2 of leukoderma. The necessary amount of bimatoprost possibly varies a little depending on each patient. We instructed the patients to apply "enough" of it without specifying a certain amount.

The primary end-point was assessment of repigmentation by dermatologists after a 6-month course of bimatoprost application on a scale of 0–3 (0, "no change"; 1, "slightly improved"; 2, "improved"; and 3, "greatly improved" compared with the skin before bimatoprost treatment). The color of the skin was also evaluated objectively by a color-difference meter, CM-2600d (Konica Minolta, Tokyo, Japan). *L** represents lightness with the darkest black at 0 and the brightest white at 100. The *a** axis represents red/green opponent colors, with green at negative *a** values and red at positive *a** values. The *b** axis represents yellow/blue opponent colors, with blue at negative *b** value and yellow at positive *b** value. The area of skin affected by leukoderma was not measured because the shape of most leukodermas was complex and the leukodermas were on the neck; the surface of the leukoderma was uneven and difficult to measure.

Because this was an exploratory study to evaluate the possibility that bimatoprost was effective for RD-induced leukoderma, we set the number of enrolled patients to approximately 10, although we realized that this number was too small to evaluate the results statistically.

Bimatoprost 0.03% solution (Lumigan; SENJU Pharmaceutical, Osaka, Japan) was purchased by Teikyo Academic Research Center, Teikyo University. This study was approved by the Teikyo University institutional review board. The study was carried out under the principles of the Declaration of Helsinki and followed the Ministerial Ordinance on Good Clinical Practice for Drugs. Written informed consent to participate in this study was obtained from each subject.

Table 1. Demographics of the 11 enrolled patients with rhododendrol-induced leukoderma

No.	Sex	Age. (years)	Duration of RD use (months)	Time to onset of RD-induced leukoderma after initiation of RD (months)	Previous treatment before enrollment in this study	Lesion	Control lesion
RD-01	F	75	27	26	Topical, Oral therapy	L neck	R neck
RD-02	F	40	27	23	Topical, Oral therapy	R neck	–
RD-03	F	54	27	22	Topical, Oral therapy	L neck	–
RD-04	F	65	24	16	Topical, Oral therapy	L neck	R neck
RD-05	F	59	33	21	Topical, Oral therapy	L neck	R neck
RD-06	F	46	2	4	Topical, Oral therapy	R neck	–
RD-07	F	45	28	28	Topical, Oral therapy	L neck	R neck
RD-08	F	69	15	15	Topical, Oral therapy	R neck	L neck
RD-09	F	58	23	23	Topical, oral therapy, and photo therapy	Dorsum of L hand	Dorsum of R hand
RD-10	F	33	23	23	Topical, Oral therapy	R neck	–
RD-11	F	65	27	27	Topical, oral therapy, and photo therapy	R neck	L neck

L, left; R, right; RD, rhododendrol.

RESULTS

All 11 enrolled patients were female, and the mean age was 55 years (range, 33–75). The mean duration of RD use was 23 months (range, 2–33). The mean time to onset of RD-induced leukoderma after initial application of RD was 19 months (range, 4–28). All patients had been treated previously with topical and oral therapies such as topical steroid or oral vitamin such as vitamin C and/or vitamin E. Two patients had received phototherapy in addition to topical and oral therapies before enrollment in this study (Table 1).

Ten patients completed the 6-month course of bimatoprost application. The score of doctors' assessment of RD-induced leukoderma treated with bimatoprost at 6 months was 0 in six patients and 1 in four patients, while the score on the control leukoderma that was not treated with bimatoprost was 0 in all patients (Table 2).

Data of the color-difference meter on leukoderma treated with bimatoprost are shown in Figure S1, and the data on leukoderma without any treatment as the control are shown in Figure S2. Box-and-whisker plots of the data of the color-difference meter on leukoderma treated with bimatoprost and those on leukoderma without any treatment as the control are shown in Figure 1. They revealed tendencies of a slight decrease in *L** value (median of amount of change, −3.2; first quartile, −5.2; third quartile, −1.2; Figs S1a,b,1a), indicating that the skin became darker, and an increase in *a** value (median of amount of change, 1.7; first quartile, −0.27; third quartile, 2.7; Figs S1c,d,1b), indicating that the skin became redder, on the skin where bimatoprost was applied, although control leukoderma also showed a tendency of a decrease in *L** value (median of amount of change, −1.5; first quartile, −4.9; third quartile, −1.2; Figs S2a,b,1a) but not an increase in *a** value (median of amount of change, 0.99; first quartile, −1.1; third quartile, 2.2; Figs S2c,d,1b). As for the *b** value, little change was observed over the 6-month period of this study both in the leukoderma treated with bimatoprost and in the

Table 2. Treatment outcome as evaluated by dermatologists after a 6-month course of treatment with bimatoprost

	Treatment evaluation by dermatologists	
No.	Lesion treated with bimatoprost	Control
RD-01	1	0
RD-02	–	–
RD-03	1	–
RD-04	1	0
RD-05	0	0
RD-06	0	–
RD-07	0	0
RD-08	0	0
RD-09	0	0
RD-10	1	–
RD-11	0	0

Assessment of repigmentation: 0, "no change"; 1, "slightly improved"; 2, "improved"; and 3, "greatly improved" compared with the skin before bimatoprost treatment.

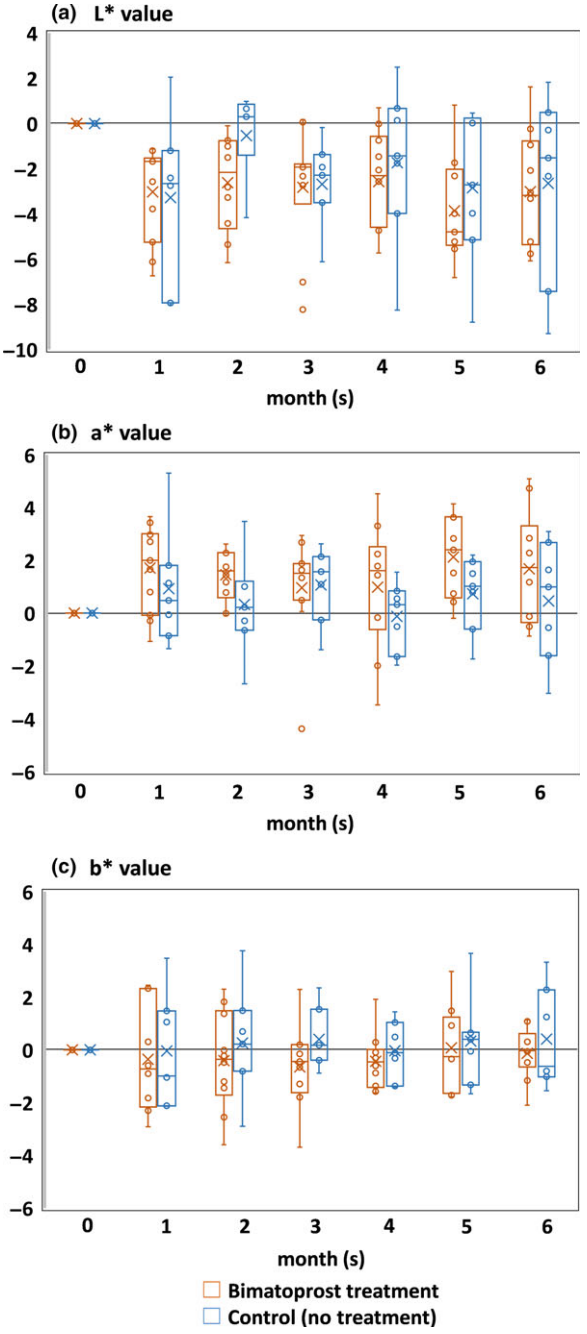

Figure 1. Box-and-whisker plots of data of the color-difference meter on leukoderma treated with bimatoprost and those on leukoderma without any treatment as a control. (a) Amount of change in *L** value compared with the value at enrollment. (b) Amount of change in *a** value compared with the value at enrollment. (c) Amount of change in *b** value compared with the value at enrollment.

control leukoderma without application of bimatoprost (median of amount of change, −0.13; first quartile, −0.43; third quartile, 0.43; median of amount of change, 0.41; first quartile, −0.91; third quartile, 1.77, respectively; Figs S1e,f,S2e,f,1c).

Representative cases that showed repigmentation after bimatoprost application are shown in Figure 2.

As for safety, during the study period, three patients complained of slight erythema on the bimatoprost-applied lesion, and one of them also felt pruritus. Another patient complained of pruritus without erythema. All of these signs and symptoms were temporary and disappeared in a short period, and did not lead to discontinuation of bimatoprost application. No serious adverse events or treatment-emergent adverse events were reported.

DISCUSSION

In four out of the 10 patients, a 6-month course of bimatoprost application brought slight improvement in RD-induced leukoderma by dermatologists' evaluation, whereas there was no improvement in control leukoderma of all patients. Objective assessment by a color-difference meter demonstrated that RD-induced leukoderma had a tendency of becoming redder by bimatoprost application, and that it showed a tendency of darkening regardless of bimatoprost application in 6 months. There was little change in b^* values both in the bimatoprost-treated leukoderma and in control leukoderma. This discrepancy between subjective evaluations by dermatologists and objective assessment by a color-difference meter might have occurred because objective assessments did not include measurement of the area due to unevenness of the area affected by leukoderma. Some cases evaluated as improved by dermatologists showed shrinking of leukoderma from the edge of the area affected by leukoderma, and the others showed repigmentation around follicles.

The reasons that only four patients showed slight effectiveness of bimatoprost on RD-induced leukoderma may be that the enrolled patients had been refractory to previous treatment, the duration of bimatoprost application was too short, and the lesion of leukoderma was on the neck or hand. It has been reported that repigmentation was more frequently observed on the face than on the neck or the hands.[3] Hair follicles are considered to serve as reservoirs of melanocytes,[23] and the density of follicles in the face is higher than that in the arms.[24] In accordance with this theory, acral lesions of vitiligo are indeed resistant to therapy.[25] Kuroda *et al.*[26] reported that brown and black guinea pigs exposed to RD demonstrated repigmentation spontaneously after discontinuation of RD exposure. They proposed that melanocyte stem cells migrated from bulge, secondary hair germ or surrounding epidermis, and differentiated into melanocytes in addition to the presence of residual epidermal melanocytes. In the patients enrolled in our study, there might have been few or no residual epidermal melanocytes which possibly could have reacted with bimatoprost, besides

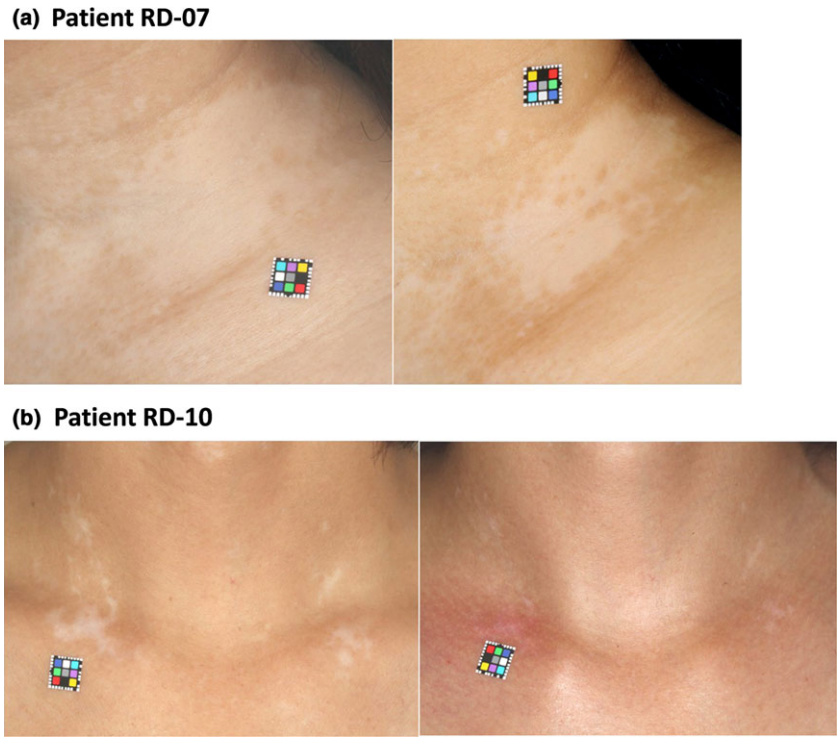

Figure 2. Representative cases who showed repigmentation after bimatoprost application. (a) Patient RD-07. Left panel, before bimatoprost application; right panel, after bimatoprost application for 6 months. (b) Patient RD-10. Left panel, before bimatoprost application; right panel, after bimatoprost application for 6 months.

the lower number of follicles in the neck or the hand than in the face. The fact that only 2% of individuals who used skin-whitening products containing RD showed RD-induced leukoderma indicates that susceptibility to RD may be associated with genetic factors in melanocytes or tyrosinase. Moreover, Inoue *et al.*[1] reported that 61.5% of Japanese patients who used prostaglandin F2α analogs noticed eyelid pigmentation for a mean of 67.6 months. Skin pigmentation does not occur in all patients using prostaglandin F2α analogs. Further studies are required to elucidate susceptibility to RD-induced leukoderma and pigmentation caused by bimatoprost.

The color-difference meter demonstrated that RD-induced leukoderma had a tendency of darkening regardless of bimatoprost application in 6 months. We cannot rule out the possibility that patients with RD-induced leukoderma gained repigmentation spontaneously regardless of bimatoprost application, or that patients applied bimatoprost to both sides contrary to our instructions although applied lesions should also become redder. A larger trial is required to elucidate this. In order to assess the contribution of suntan, we evaluated data of the color-difference meter on the skin where bimatoprost was applied in each calendar month (Fig. S3). L^* values had a tendency to decrease in winter when the impact of the sun is the least, suggesting minimum impact of the sun on our results. We did not instruct the patients about the use of sunscreen at the beginning of this study; however, patients using RD were so eager to whiten their skin that we can speculate that they always used sunscreen.

As for safety, all adverse events that occurred on the neck were mild and temporary, improved without any intervention and did not recur. All adverse events occurred on the neck. Their association with bimatoprost was not definitive. Although no serious adverse events or treatment-emergent adverse events occurred, we cannot make a conclusion about the safety of bimatoprost application on RD-induced leukoderma from this study due to the small number of patients and the short period of bimatoprost application of 6 months.

This pilot study suggests the possibility that bimatoprost is effective for RD-induced refractory leukoderma. However, larger studies are necessary to better assess the effectiveness of bimatoprost on RD-induced leukoderma.

CONFLICT OF INTEREST: We received grant for this research from Kanebo Cosmetics Inc.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Data of the color-difference meter on the skin where bimatoprost was applied.

Figure S2. Data of the color-difference meter on control leukoderma.

Figure S3. Data of the color-difference meter on the skin where bimatoprost was applied at calendar month.