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REVIEW ARTICLE

Rhododendrol-induced leukoderma update I: Clinical findings and treatment

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Abstract

Individuals who used skin-whitening cosmetics (quasi-drugs) containing 2% rhododendrol-containing agents, developed leukoderma at a higher frequency than those who have used other skin-whitening cosmetics. The Rhododenol Research Team (RD-Team) was formed and commissioned by Kanebo Cosmetics Inc. to conduct research in treatments of rhododendrol-induced leukoderma (RDL), to evaluate effective treatment options from a medical standpoint, and provide information to a wide range of people. In this study, we evaluated the efficacy of various treatments for RDL from a medical perspective, based on the information published in the literature as original or review articles. We searched the PubMed (international) and the Igaku Chuo Zasshi (ICHUSHI) (Japanese) databases using the keywords "Rhododenol" and "rhododendrol", for articles published between July 2013 and November 2020. We discuss the main clinical findings and treatments (topical, oral, phototherapy, and surgical) of this condition based on the literature review. We found that ultraviolet light therapy is the most effective treatment for RDL. We have also summarized reports of the efficacy of oral vitamin D3 in RDL. A topical prostaglandin derivative has been reported in a new study to be effective. We have provided guidance for patients using self-tanning and skin-whitening agents to improve their quality of life. Finally, we have highlighted the importance of providing patients with information on contact dermatitis and instructing them to discontinue product use immediately if they develop any symptoms of contact dermatitis while using skin-whitening agents.

KEYWORDS
epidemiology, melanin, melanocyte, prognosis, treatment

1 | INTRODUCTION

Rhododendrol (RD) (chemical name, 4-(4-hydroxyphenyl)-2-butanol; proprietary name, Rhododenol) is a melanin production inhibitor (a skin-whitening agent) developed independently by Kanebo Cosmetics Inc. (Figure 1). Individuals who used skin-whitening cosmetics (quasi-drugs) containing 2% RD-containing cosmetics developed leukoderma at a higher frequency than those who used other skin-whitening cosmetics. Thus, in July 2013, the marketing authorization holder issued a voluntary recall globally. In a survey conducted by the marketing authorization holder, 19 606 individuals developed symptoms (as of November 30, 2020, including 11 919 individuals who completely or almost completely recovered). It is estimated that approximately 800 000 consumers used the cosmetic in question, which equates to an incidence rate of 2.4% for leukoderma.[1]

The Japan Dermatological Association established the Special Committee on the Safety of Cosmetics Containing Rhododenol on July 17, 2013. The committee undertook activities to ascertain the condition of rhododendrol-induced leukoderma (RDL) to provide accurate information to medical professionals (dermatologists) and patients, to investigate the pathology, and to establish diagnostic and treatment methods at the earliest possible stage. The committee conducted three nationwide surveys,[2–4] prepared medical care guides for medical professionals,[5] and prepared 'frequently asked questions' for patients. Fulfilling its role, the committee published the results of the survey as a lecture accessible to the public on May 31, 2015. However, there remains a strong demand for information from patients with intractable conditions. Therefore, in July 2016, the Rhododenol Research Team (RD-Team) was formed and commissioned by Kanebo Cosmetics Inc. to conduct research in the treatment options for RDL, evaluate effective treatments from a medical standpoint, and provide information to a wide range of people.

Literature, previously published as original or review articles, were sought out and investigated by the members of the RD-Team. The results of the first phase of research, conducted from July 2016 to March 2018, have been summarized and reported.[1] The present report summarizes the results of national and international original or review articles published between July 2013 and November 2020. We searched the PubMed database for international articles and the Igaku Chuo Zasshi (ICHUSHI) (Japanese) database for Japanese articles using the keywords "Rhododenol" and "rhododendrol". We believe that this information will be useful for the treatment of patients with RDL.

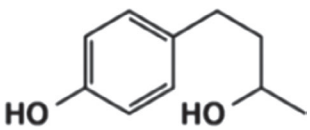

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FIGURE 1 The chemical structure of rhododendrol. The chemical name is 4-(4-hydroxyphenyl)-2-butanol, and the proprietary name is Rhododenol

2 | CLINICAL FINDINGS AND TREATMENT

2.1 | Clinical course of onset and diversity of symptoms and recovery

According to the results of nationwide surveys conducted by the Japan Dermatological Association Special Committee on the Safety of Cosmetics Containing Rhododenol,[2–4] almost all users who developed symptoms were adult women aged ≥30 years, given that the product inducing the symptoms was a skin-whitening cosmetic, and the largest consumers were women in their 60 s. As this condition was detected in 2.4% of the users, factors related to the patients' backgrounds, such as occupation, and the use of other skin-whitening agents, were examined; however, no relevant factors were found.[1] Initially, a thyroid autoantibody was presumed to have a high prevalence in patients with this disease; however, the age-matched study conclusively proved that there was no significant difference between the healthy and RDL-affected groups.[2]

The frequency of the condition increased between July and August; however, this may be attributed to factors such as an increase in the use of these cosmetics from early spring, and tanning of the surrounding healthy skin, making the onset of leukoderma more obvious.[2] One of the reasons for the underlying RD-induced melanocyte damage is that RD becomes a substrate for tyrosinase. The RD metabolites produced were found to cause melanocyte damage in melanosomes.[6] Therefore, increased tyrosinase activity due to ultraviolet (UV) radiation in summer might have enhanced RD melanocyte dysfunction, thereby inducing leukoderma development.[2]

In 96% of patients, the leukoderma site matched the area where the product was used, whereas, in 4% of patients, leukoderma also occurred in areas where no product was applied. In the first nationwide epidemiological survey,[2] incomplete leukoderma was observed in approximately 50% of the RDL patients, approximately 20% had complete leukoderma, and approximately 30% had a mixture of both. Results from the second nationwide epidemiological survey[3] were comparable; 50% of the patients showed predominantly incomplete leukoderma, 25% showed a predominantly complete leukoderma, and 25% showed a mixed type.

As cosmetics were mostly skin-whitening agents, most patients had incomplete leukoderma with different shades observed in the face and neck. Furthermore, as patients tended to apply the product on their fingers prior to application to the face and neck, and then proceeded to apply any excess on the hands and forearms, several patients also developed leukoderma on their hands, between their fingers, and on their forearms.

Approximately 40% of patients experienced inflammatory symptoms, such as erythema and pruritus prior to the onset of leukoderma, suggesting the involvement of allergic contact dermatitis induced by RD. When a patch test was performed using 2% RD in the petrolatum, a positive reaction was observed in 13.5% (25/185) of the patch-tested patients, and in approximately 20% (20/100) of patients who experienced inflammatory symptoms before the onset of leukoderma.[5] The positive rate in patients without inflammation

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was 6.8% (5/74).[5] There was no patient with allergic contact dermatitis to RD who did not develop leukoderma. It was suggested that these patients had RD sensitization, which appeared to have an association with the onset of RDL. However, 86.5% of the RDL patients were not sensitized to RD, indicating no direct association with the onset of RDL.

This condition was characterized by a marked pigment enhancement following the discontinuation of the use of RD-containing cosmetics in approximately 40% of the patients, whether treated or untreated.[4,5] In the third nationwide epidemiological survey conducted 1 year and 5 months after the cases first occurred, the symptoms had improved in 82% of the patients; however, these were unchanged or worsened in 16% of the patients.[4] In some cases, the increased pigmentation that developed during the course of the disease did not disappear, suggesting that some cases were intractable. There were also cases where leukoderma appeared in sites other than those where the RD-containing cosmetics were applied after the initial onset of the disease, and were suspected to be cases of vitiligo. Observing the progress of symptoms in each area, the rate of leukoderma remission was highest in facial leukoderma, followed by that on the neck, and finally on the hands. Several cases of remission were seen in patients with residual spots of leukoderma matching the pores even after the pigment was regenerated.[4]

2.2 | Clinical findings and morphological characteristics

This section focuses on the differentiation of this condition from vitiligo, which is one of the most important processes clinically. RDL occurs following the application of RD-containing cosmetics, usually on the face, neck, and the back of the hands, causing a clinical scenario comprising of a mixed incomplete leukoderma and complete leukoderma.[2,5] The pigment is partially or completely regenerated following discontinuation of RD-containing cosmetics application in approximately 80% of cases.[4] Clinical features of RDL include relatively indistinct margins, partially mottled leukoderma, and the absence of the Koebner phenomenon (Figure 2).[2]

However, there were patients in whom leukoderma spread after the discontinuation of the RD-containing cosmetics, or appeared in areas where the cosmetic was not applied. These cases were, therefore, difficult to differentiate from vitiligo (Figure 3).[2–5] The third nationwide survey reported that 14% of patients had leukoderma at sites where the product was not applied.[4,7] Extreme care was necessary for the diagnosis, particularly when symmetric complete leukoderma was observed. In fact, RDL and vitiligo could be differentiated in only 15% of the respondents in the first nationwide survey.[2] Histological analysis of the RD-containing cosmetics application site revealed pigmentary incontinence in the dermis and an association with melanophage infiltration in the leukoderma-affected area, as well as in areas with residual pigment; however, this was not prominent in vitiligo.

Immunohistochemical staining of Melan-A, HMB45, and other markers revealed the presence of residual melanocytes in 27 of 31 RDL cases, although it did depend on the timing of the biopsy.[8] In an analysis of 149 cases of RDL, Yoshikawa et al[9] reported that leukoderma occurred more frequently at sites other than the cosmetic application sites in patients with a history of atopic dermatitis. One of the features of RDL is that inflammatory cells infiltrating the RDL area are predominantly CD4(+) T cells rather than CD8(+) T cells; these cells are relatively dense and are detected in the upper layer of the dermis and around the hair follicle structures.[5,8]

Conversely, the results of specimen evaluation using electron microscopy in 13 cases of RDL and six cases of vitiligo indicated that the retention of melanocytes in the leukoderma lesion and inhomogeneous melanization in melanocytes and denatured melanosomes were findings specific to RDL.[10] Another study reported that melanosome transport was not impaired, and fibroblasts containing melanosome globules and melanophages were detected in the dermis.[8] Therefore, the detection of intact intracellular organelles in RDL

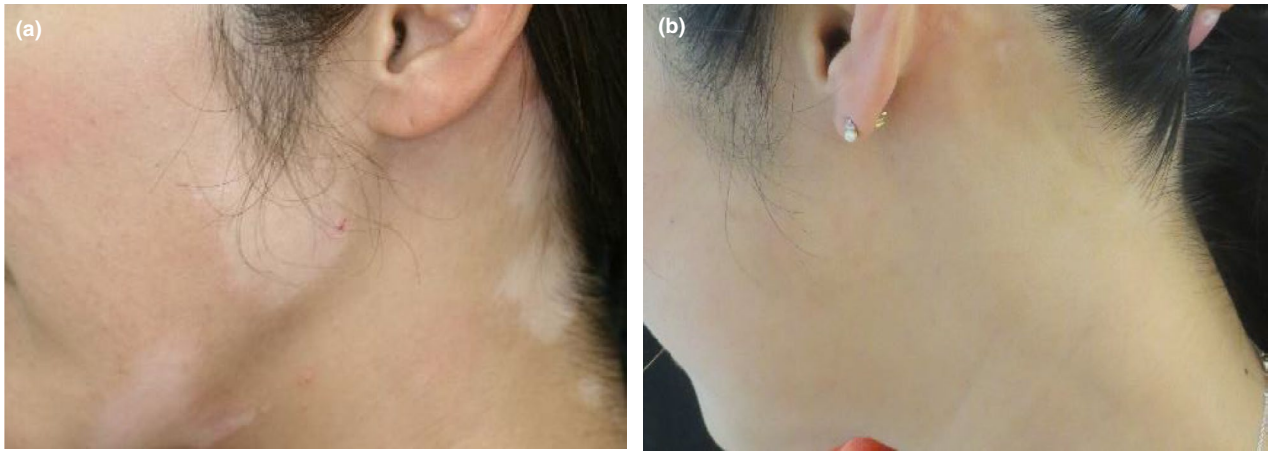

FIGURE 2 A typical case of rhododendrol-induced leukoderma with good prognosis, who was cured within one and a half years. (a) The clinical features at the first visit are shown. Relatively indistinct margins, partially mottled leukoderma, and absence of the Koebner phenomenon were seen. (b) The patient was cured after one and a half years

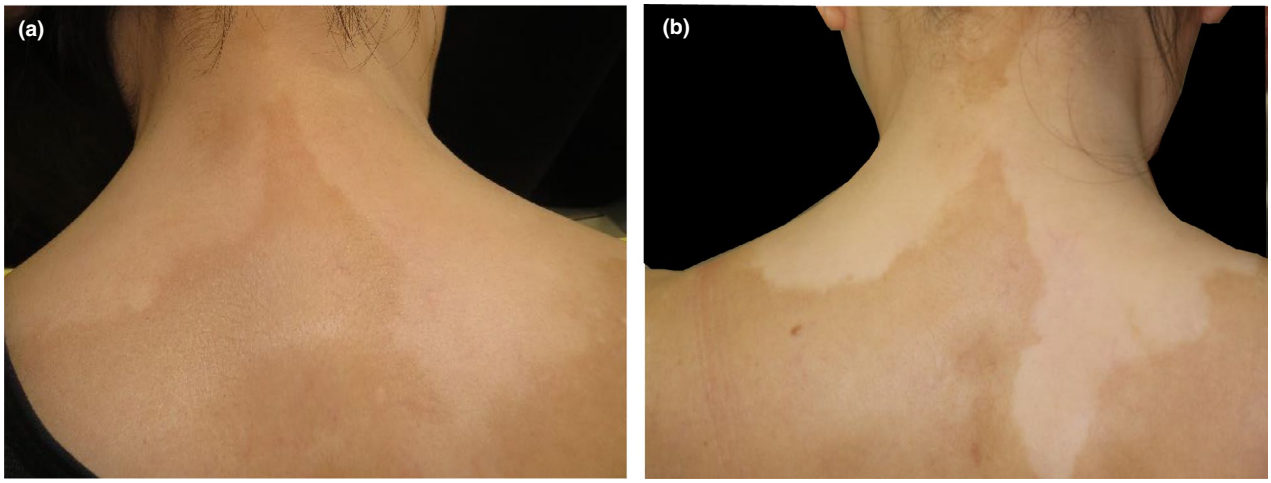

FIGURE 3 A typical case of rhododendrol-induced leukoderma with a prolonged course, who developed leukoderma in areas where rhododendrol-containing cosmetics were not applied, after developing leukoderma in areas where rhododendrol-containing cosmetics were applied. (a) The clinical features at the first visit are shown. (b) The patient was not improved after one and a half years

cases was consistent with the reversible clinical course observed in the majority of cases.

Repigmentation from hair follicles, often observed in vitiligo, is thought to develop as a result of the recoloration of inactive immature melanocytes present in the hair follicles.[11] In an analysis of 11 RDL patients, Watanabe et al[12] reported that MITF-positive Frizzled-4 positive melanocyte stem cells (FZD4+/MITF+) remained in the hair follicle bulge, regardless of the severity of the condition, and may assist in the diagnosis. Moreover, the numbers of melanocyte stem cells and mature melanocytes (FZD4−/MITF+) in the hair follicles of RDL patients were lower than those in both peripheral sites and lesions, and no immature melanocytes were observed in patients with predominantly complete leukoderma, or in those with a recovery rate of <50% after 1 year of the initial diagnosis.[13]

2.3 | Treatment and therapeutic effects

To date, various treatments have been adopted based on treatment protocols for vitiligo, primarily in intractable cases. However, it should be noted that this report on the efficacy of RDL treatments has not been evaluated rigorously; 65% of cases tended to improve without treatment after discontinuation of application, and a number of attempted treatments were clinical trials without a control. However, the results of the third nationwide survey,[4] which assessed the therapeutic effects based on inputs from doctors who had treated the condition and affected patients, indicated that the evaluation by the doctors and the patients correlated to a certain extent; therefore, this information should be helpful.

Although topical therapy is prescribed for this condition, the quantity and frequency of its application are unclear, and improvement seen by this treatment would be difficult to distinguish from improvement resulting from the natural course of the condition. Conversely, several reports on oral therapy, UV light, and surgical therapy included intractable cases, where no pigment regeneration was observed. Furthermore, in reports indicating that these treatments are effective in clinical trials without a control group, the effect could, therefore, be attributed to treatment. Similar results were also obtained from our survey, which was conducted 2 years after the third nationwide survey.

2.3.1 | Topical agents

In the third nationwide survey, of the 255 patients who used activated vitamin D3 (vitamin D3 ointment), 24%, 30%, and 43% reported that the treatment was effective, ineffective, and the results were indeterminable, respectively. Of the 469 patients who used tacrolimus ointment, 38%, 23%, and 34% reported that the treatment was effective, ineffective, and the results were indeterminable, respectively. Of the 288 patients who used topical steroids, 42%, 27%, and 29% reported that the treatment was effective, ineffective, and the results were indeterminable, respectively.[4] Of the patients with RDL, 43.8% exhibited symptoms associated with inflammation, including pruritus and erythema, and 13.5% showed a positive result in the patch test for RD;[5] thus, tacrolimus ointment and topical steroids are considered to be effective in this condition. There was some difference in the efficacy rate in our survey as well; however, these treatment options seem to be useful in at least some cases.

Fukaya et al[14] reported the results of an open-label pilot study investigating topical bimatoprost, a prostaglandin derivative, as a novel therapy. Reportedly, the application of 0.03% bimatoprost solution in patients with intractable RDL remaining on the neck or back of the hands, for 6 months resulted in a marginal improvement in four out of ten patients. One patient for whom the treatment

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was effective continued with a long-term application for another year and exhibited sustained improvement.[15] Additionally, a clinical study[16,17] demonstrated the benefits of topical prostaglandin derivatives in vitiligo. Furthermore, it has been suggested that combining this treatment with UV light increases its efficacy.[18,19] Although these results are preliminary, clinical research on drugs that activate pigment cells are expected to progress further in the future.

2.3.2 | Oral therapy

Watabe et al[20] divided 48 patients with refractory RDL into two groups and examined the effects of oral vitamin D3 treatment (cholecalciferol 5000 IU once daily for 5 months). Patients with intractable leukoderma were identified by the onset of leukoderma during RD use, with no change, or worsening of conditions after discontinuation of RD application, and resistance to treatment for at least 6 months. The effect was evaluated independently by three dermatologists, who assessed the condition of leukoderma in patients before and after administration. Each patient was given a score of "1" for improvement, "0" for no change, and "−1" for worsening. The condition worsened in six out of 23 patients in the non-treatment group, while none of 22 patients in the treatment group experienced worsening symptoms, and 18 patients showed improvement of leukoderma symptoms. A positive correlation was observed between the blood 25 (OH) vitamin D3 level and the degree of improvement of vitiligo symptoms after oral administration for 5 months.[20] Considering that this was a study targeting advanced and worsening cases, indicated by the fact that six patients exhibited worsening of symptoms in the non-treatment group,[20] this treatment is expected to be somewhat effective.

Sano et al reported that some cases improved with the administration of vitamin C alone, or in combination with tranexamic acid. However, there were a limited number of cases in each group, and there was no significant difference in the degree of improvement, due to differences in the treatment methods.[21]

2.3.3 | Phototherapy

While some studies reported no significant effects, other studies reported that phototherapy has been effective. Masui et al reported that five out of seven intractable cases (71%) improved following phototherapy (unpublished data 2015). Kuwahara et al reported that the area affected by leukoderma was reduced in ten out of 13 intractable cases upon treatment with excimer light; and this, in combination with vitamin D3 ointment application, helped prevent uneven coloration during pigment regeneration.[22]

According to the third nationwide survey, approximately 16% of patients received UV light therapy. The physicians determined that this treatment exhibited approximately 52% efficacy in facial leukoderma and 29% effectiveness in leukoderma on the back of the hands, while in the survey requesting input from both doctors and patients, 63% of doctors and 59% of patients responded that UV light therapy was effective (Figure 4).[4]

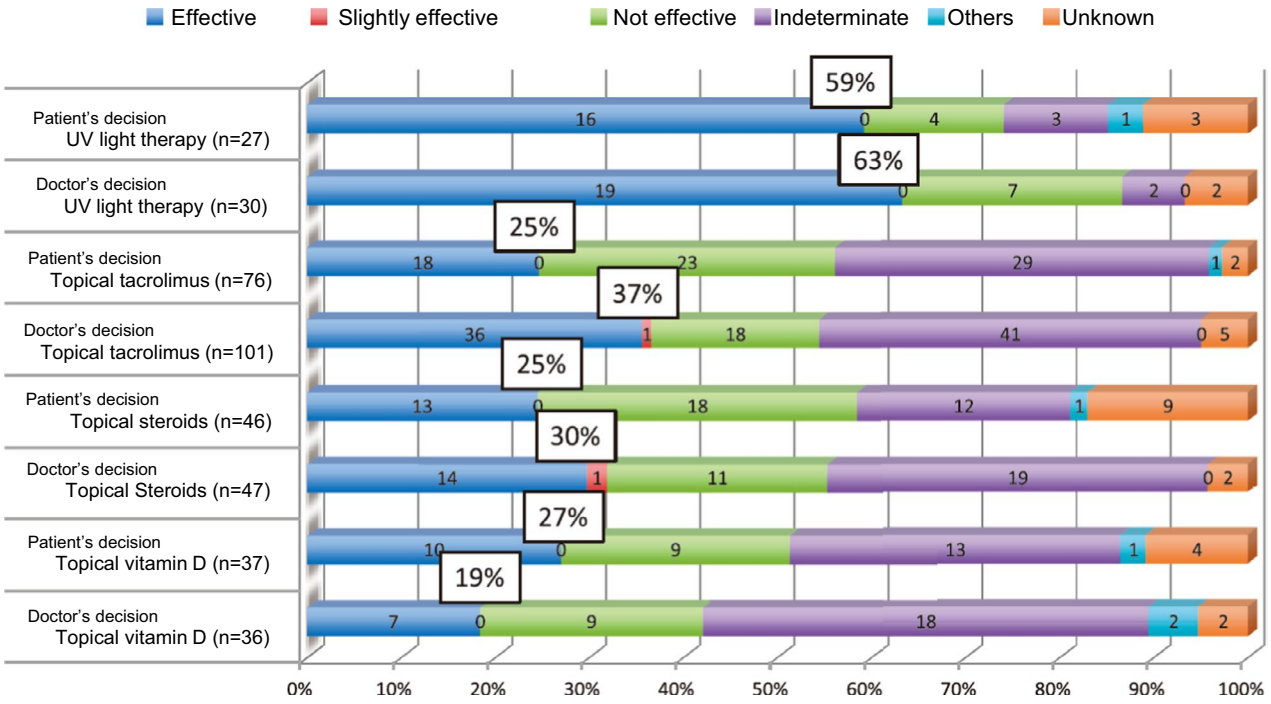

FIGURE 4 A comprehensive evaluation of doctors and patients for the treatment of rhododendrol-induced leukoderma (referred and partially modified from figure 31 of ref. 4 (UV, ultraviolet)

2.3.4 | Surgical treatment

Surgery has been reported as a trial treatment of this condition. Kuwahara et al[22] reported a case in which the combination of a mini-graft and excimer light irradiation was markedly effective.

2.3.5 | Future treatments

Currently, it is expected that several new drugs and treatment options, including Janus kinase inhibitors and autologous epidermal transplantation, which are reported to be effective in vitiligo, will be available for clinical application in the near future. We hope that therapeutic modalities may be effective in patients who do not respond to existing therapies.

3 | PATIENT GUIDANCE

3.1 | Points for patient guidance

According to the third nationwide survey conducted 18 months after the voluntary recall, patients whose conditions had completely healed, almost healed, or had improved, accounted for more than 80% of cases of RDL.[4] Therefore, for patients who are concerned about the prognosis, it should be first explained that the disease usually improves once the patient stops using RD-containing cosmetics. It is also useful to explain the mechanism underlying leukoderma onset and progression in simple terms, explaining that RD metabolites cause melanocyte dysfunction and that immunological mechanisms may be involved in the induction of leukoderma. Explaining that the mechanisms underlying leukoderma vary among individuals, which implies that the onset and severity also differ from person to person, may also be effective.

Rhododenol has been shown to impair melanocytes in a tyrosinase-dependent manner.[6,23] Furthermore, UV irradiation reportedly increases the cytotoxicity of RD.[24] Therefore, while the applied RD remains on the skin, it is advisable to avoid exposure to UV light as it increases the tyrosinase activity. However, RD is metabolized to RD quinone by tyrosinase, and therefore, may not remain on the skin for an extended period. Hence, it is unlikely that UV light will induce leukoderma deterioration at this point, more than 6 years after its voluntary recall. It has been demonstrated that UV light therapy is effective in treating RDL in patients having long-term conditions.[22] In UV therapy, the leukoderma site is exposed to a limited magnitude of UV radiation, which is effective for treatment at a fixed dose. Conversely, the UV light we are exposed to in daily life affects both the leukoderma site and the area with residual pigments. Therefore, when the area with residual pigment is exposed to UV light, the transient pigment enhancement around the leukoderma site that occurs during the pigment recovery process may worsen, which could create a noticeable contrast between the pigment-regenerating area and the leukoderma area. Therefore, the daily use of sunscreen is recommended. Moreover, as the remaining leukoderma-affected area has no protection from UV light owing to the lack of melanin, it is vital to shield the area from UV light to prevent photoaging of the skin and malignant tumors.

3.2 | Guidance for improving quality of life using camouflage cosmetics and tanning cosmetics

Quality of life (QOL) is reduced in patients with RDL, as the lesions are primarily located on exposed, visible areas, such as the face, neck, and backs of the hands. Furthermore, pigment regeneration in leukoderma sites takes time.[25] Providing guidance on using camouflage cosmetics has been reported to improve the QOL in vitiligo,[26,27] and the same may also be useful for improving the QOL of RDL patients.[25] It often takes longer for the pigment to regenerate on the neck and the back of the hands as compared to that on the face; however, applying cosmetic makeup to these areas is often unsatisfactory because the makeup stains clothes and hand washing might remove the makeup. Therefore, for such areas, using self-tanning products, which are more resistant to wear and water, may be effective. A recent study demonstrated that creams containing dihydroxyacetone, which are easy to apply and able to retain moisture, resulted in a significant improvement in the QOL scores of Skindex-16 after a 2-month application period.[28] Moreover, self-tanning cosmetics containing dihydroxyacetone (Dhadress; Grafa Laboratories) can be used in parallel with UV light therapy using narrow-band UVB.[25]

3.3 | Guidance on the use of other skin-whitening agents

Rhododendrol-induced leukoderma patients often have enhanced pigmentation around the leukoderma sites. A certain number of patients wish to use skin-whitening agents in areas where pigmentation is enhanced due to the noticeable contrast. Therefore, doctors should understand the following concept and explain this information to patients.

Skin-whitening agents are approved as active ingredients of quasi-drugs used to “prevent spots and freckles formed due to sun exposure” and “suppress melanin production and prevent the formation of spots and freckles” in Japan.[29] These skin-whitening agents are broadly classified into four types based on their efficacy.[30] The first type acts on tyrosinase, which is used for melanin synthesis in pigment cells, and inhibits activity and maturation or promotes metabolic degradation. These products include ascorbic acid derivatives, arbutin, kojic acid, and rucinol, and RD are included in this group. The second type suppresses melanocyte growth factors and inflammatory mediators induced by UV exposure. These products include chamomile extract and tranexamic acid. The third type primarily acts through the suppression of melanin diffusion in the epidermis and promotion of melanin excretion and includes products

such as niacinamide and 4-MSK (potassium 4-methoxysalicylate). The fourth type inhibits the polymerization reaction of melanin and includes products such as ethyl ascorbic acid.

The action of these skin-whitening agents is considered to induce reversible reactions, with reversal to the original state observed after the application is discontinued. However, in some patients, RD caused irreversible reactions, resulting in residual leukoderma even after the discontinuation of cosmetic use. These types of infrequent adverse reactions cannot be predicted with pre-launch studies and may only become apparent when a large number of people use the product. Particular care is needed with the first type of skin-whitening agent, which exerts the same effect as RD, as these products may cause similar adverse reactions. When treating patients with leukoderma caused by the use of skin-whitening agents, we physicians must explain to patients that any skin-whitening agents may cause leukoderma through unpredictable mechanisms.

There are several reports of contact dermatitis caused by kojic acid, rucinol, and arbutin.[31] Although previous reports do not provide evidence that leukoderma occurred in such cases of contact dermatitis due to the use of skin-whitening agents, 13.5% of all RDL patients also had allergic contact dermatitis.[5,32] Hence, it is possible that the appearance of leukoderma may be triggered by contact dermatitis. Therefore, it is advisable to provide patients with information on contact dermatitis in advance and instruct them to discontinue product use immediately if they develop any symptoms suggestive of contact dermatitis while using skin-whitening agents.

4 | CONCLUSION

We found that ultraviolet light therapy is the most effective treatment for RDL. We have also summarized reports of the efficacy of oral vitamin D3 in RDL. A topical prostaglandin derivative has been reported in a new study to be effective. We have provided guidance for patients using self-tanning and skin-whitening agents to improve their QOL. Finally, we have highlighted the importance of providing patients with information on contact dermatitis and instructing them to discontinue product use immediately if they develop any symptoms of contact dermatitis while using skin-whitening agents.

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CONFLICT OF INTEREST

This research was carried out with funding from Kanebo Cosmetics Inc. There are no other conflicts of interest to declare.

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