Kasamatsu S, Hachiya A, Nakamura S, Yasuda Y, Fujimori T, Takano K, Moriwaki S, Hase T, Suzuki T, Matsunaga K.	Depigmentation caused by application of the active brightening material, rhododendrol, is related to tyrosinase activity at a certain threshold.	J Dermatol Sci.	76(1)	16-24	2014
Kuroda Y, Takahashi Y, Sakaguchi H, Matsunaga K, Suzuki T.	Depigmentation of the skin induced by 4-(4-hydroxyphenyl)-2-butanol is spontaneously re-pigmented in brown and black guinea pigs.	J Toxicol Sci.	39(4)	615-23	2014
Yagami A, Suzuki K, Morita Y, Iwata Y, Sano A, Matsunaga K.	Allergic contact dermatitis caused by 3-o-ethyl-L-ascorbic acid (vitamin C ethyl).	Contact Dermatitis.	70(6)	376-7.	2014
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森田 雄介, 矢上 晶子, 伊佐見 真実子, 西村 景子, 佐野 晶代, 鈴木 加余子, 松永 佳世子	藤田保健衛生大学病院における2006～2010年の職業性接触皮膚炎の38例のまとめ	J Environ Dermatol Cutan Allergol	8(2)	80-87	2014
森田 雄介, 矢上 晶子, 鈴木 加余子, 佐野 晶代, 松永 佳世子	Japanese standard allergen seriesにおけるゴム関連アレルゲンmix陽性21例の臨床的検討	J Environ Dermatol Cutan Allergol, 8(J Environ Dermatol Cutan Allergol	8(3)	167-174	2014
西 和歌子, 矢上 晶子, 西村 景子, 佐野 晶代, 安部 正通, 高橋 正幸, 松永 佳世子	香粧品パッチテスト2011年のまとめ	J Environ Dermatol Cutan Allergol	8(4)	255-263	2014

Ⅳ．研究成果の刊行物・別刷

皮膚病診療
Vol.37, No.1
＜別　刷＞

ロドデノール誘発性脱色素斑

松永佳世子

㈱協和企画

皮膚病診療：37(1)；6～13, 2015

topics

ロドデノール誘発性脱色素斑

松永佳世子*

Key words
ロドデノール誘発性脱色素斑，美白剤，化粧品，白斑

はじめに

ロドデノール（以下，RD）誘発性脱色素斑（Rhododenol-induced leukoderma）とは，RD含有化粧品を使用後，主に使用部位に生じるさまざまな程度の脱色素斑で，使用中止により一部あるいは全体に色素再生がみられることが多い[1]（**図1**）．

RD：Rhododenolは商品名で，一般名はロドデンドロール（rhododendrol），別名に4-（4-ヒドロキシフェニル）-2-ブタノールなどがある．本剤は，2008年1月，「メラニン生成を抑え，しみ，そばかすを防ぐ効果を有する」新規医薬部外品有効成分として，厚生労働省の認可を取得した．本剤を配合した化粧品を使用した人の中に色素脱失をきたした症例が複数確認された結果，2013年7月4日に株式会社カネボウ化粧品，ならびに関連会社の株式会社リサージ，株式会社リサップは本剤を含むすべての化粧品（**図2**）を自主回収に踏み切った．

日本皮膚科学会は，その責任ある立場から，症例の実態調査を行い，医療者（皮膚科医）と患者向けに正しい情報を提供し，診断と治療方法を早急に確立するために「ロドデノール含有化粧品の安全性に関する特別委員会（委員長：松永佳世子）」を2013年7月17日に発足し活動してきた．特別委員会は患者のためにFAQ[2]，医療者（皮膚科医）向けの診療の手引き[1,3]を作成し，一次，二次全

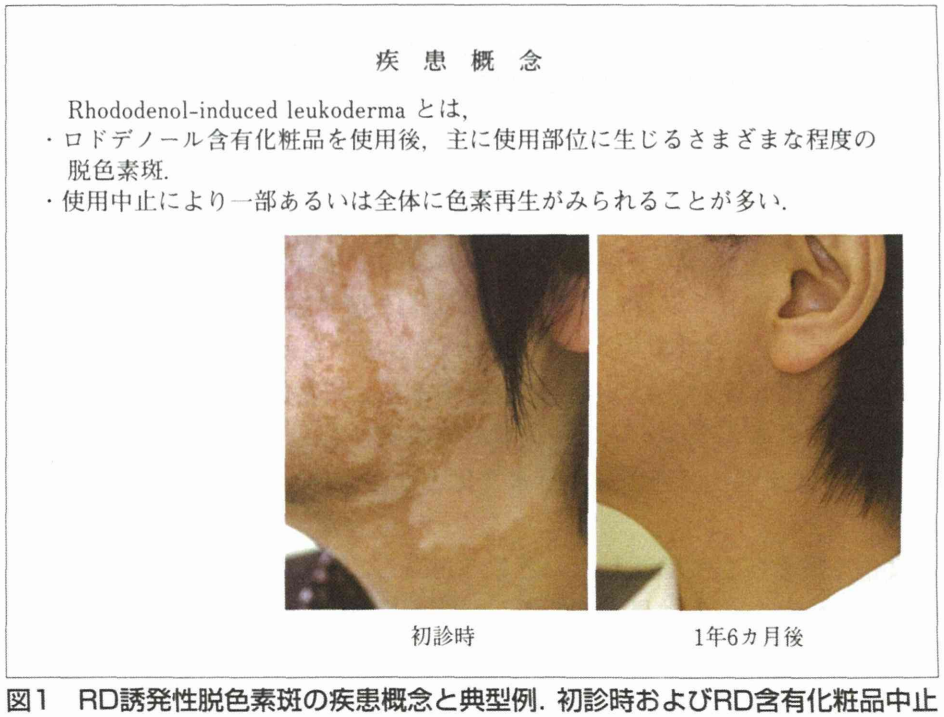

図1　RD誘発性脱色素斑の疾患概念と典型例．初診時およびRD含有化粧品中止後1年6カ月後の回復時臨床像．

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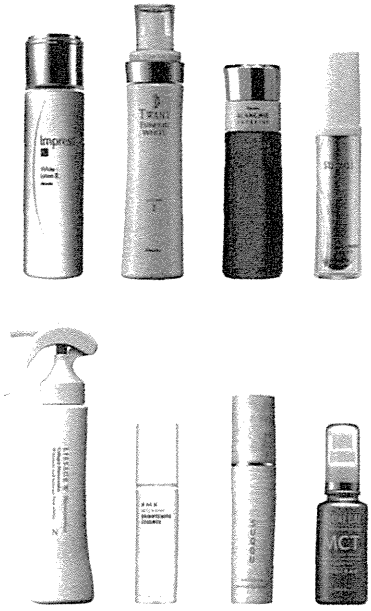
ロドデノール含有化粧品

対象製品名

【株式会社カネボウ化粧品】
<カネボウブランシール スペリア>
・ホワイトディープ クリアコンディショナー 全7品
・ホワイトディープ ミルキィコンディショナー 全3品
・ホワイトディープ ナイトコンディショナー 全4品
・ホワイトディープ マスク
・ホワイトディープ UV デイプロテクター
<suisai>
・ホワイトニングエッセンス
<トワニー>
・エスティチュードホワイト ローション 全6品
・エスティチュードホワイト UV プロテクトセラム
・エスティチュードホワイト クリアタイトマスク
・センチュリー ザ・ローション 全2品
<インプレス>
・IC ホワイトローション 全2品
・IC ホワイトエマルジョン 全2品
・IC ホワイトフィットマスク 3D
・グランミュラローション
<アクアリーフ>
・MCT ホワイトニングエッセンス

【株式会社リサージ】
<リサージ>
・ホワイト スキンメインテナイザー 全8品
・ホワイト ホワイトニング リペアクリーム
・ホワイト トライアルセット 全4品
・ボーテ サーキュリード a
【株式会社エキップ】
<RMK>
・スキンチューナー ブライトニング 全2品
・インテンシブ ブライトニング エッセンス
<SUQQU>
・ホワイトニング リペア エッセンス
・ホワイトニング ローション
・ホワイトニング バリア エマルジョン

✓上記8ブランド，54製品，2008年から販売され，国内で約25万人が利用
✓海外で約10万人が利用
✓年間売上高50億円



（上段左から）インプレス：IC ホワイトローション，トワニー：エスティチュードホワイト ローション，
カネボウブランシール スペリア：ホワイトディープ クリアコンディショナー，suisai：ホワイトニング エッセンス
（下段左から）リサージ：ホワイト スキンメインテナイザー，RMK：インテンシブ ブライトニング エッセンス，
SUQQU：ホワイトニング リペア エッセンス，アクアリーフ：MCT ホワイトニングエッセンス

図2 自主回収になったRD含有(配合)化粧品一覧

国疫学調査を施行し[4,5]，その実態と診断と治療に役立つ情報を提供してきた．また治療に役立てるための病態解明の研究を行い，その成果を日本皮膚科学会ホームページに掲載し改訂してきた[6,7]．

本稿では，RD脱色素斑について，これまでに得られた知見の概要を紹介する．

Ⅰ．RDの含まれる化粧品

RDの含まれた製品を図2に示す．詳細は厚生労働省[8]，カネボウ化粧品[9]のホームページを参照いただきたい．

Ⅱ．RDの構造と作用機序

1．発見と由来

カネボウ化粧品では，多くの植物由来のさまざまな天然物質について，メラニンの生成を抑える作用の有無をスクリーニングした結果，4(4-ヒドロキシフェニル)-2-ブタノールという物質に着目した．その後，詳しく調べたところ，メラニンの生成を抑える効果が非常に高いことが明らかになった．2008年には厚生労働省より，メラニンの生成を抑え，しみ，そばかすを防ぐ効能で医薬部外品有効成分として承認された．

2．“美白作用”を示す機序

皮膚のしみは，メラニン色素が皮膚へ過剰に沈着するため生じる．そのメラニンは皮膚に存在する色素細胞の中で合成されるが，メラニンの生成にもっとも重要な役割を果たすのがチロシナーゼという酵素である．メラニン生成反応は，チロシナーゼによるチロシンの酸化が出発点となり，その先の反応過程へと進むが，チロシナーゼはこのメラニン生成過程における律速酵素で，この反応がおこらなければ，メラニンはまったく生成されない．近年，メラニンの生成にはチロシナーゼの

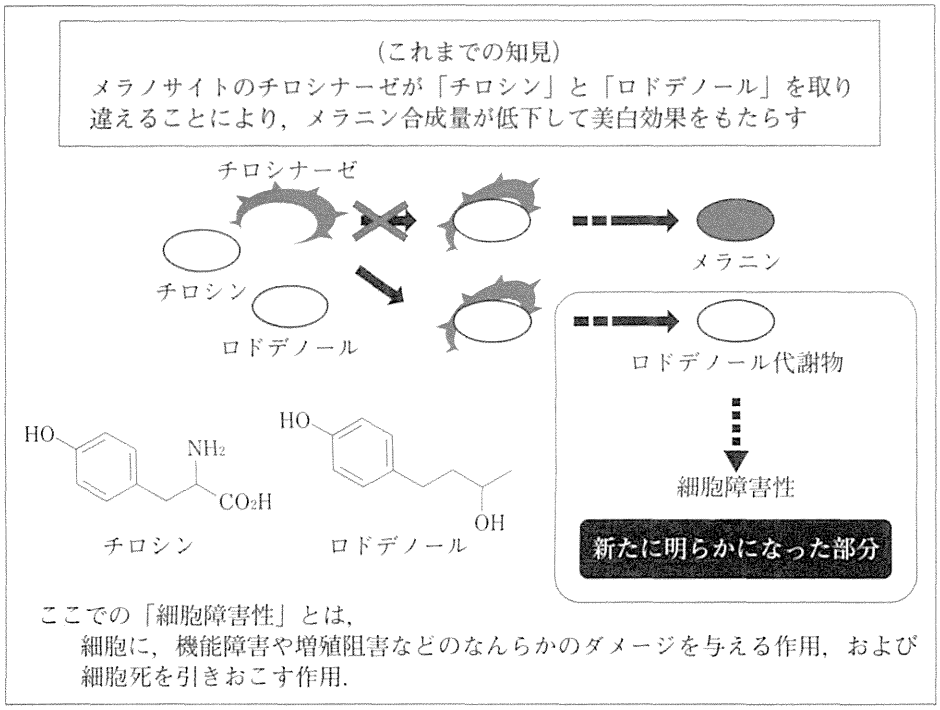


図3　RDの「美白」作用のメカニズムと細胞障害性

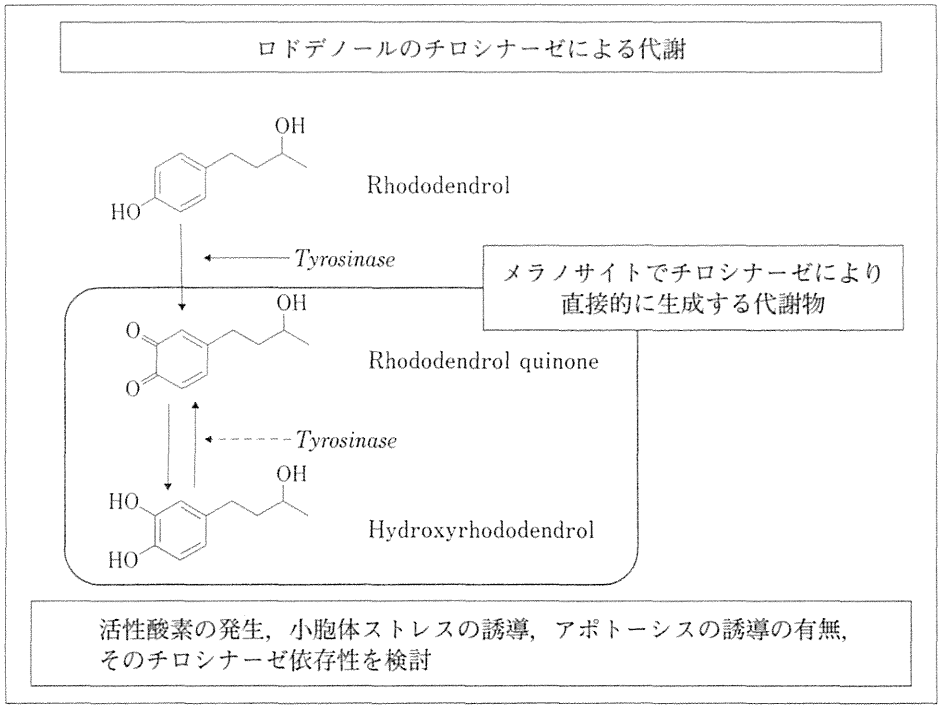


図4　RDのチロジナーゼによる代謝

みならず，2種類のチロシナーゼ関連蛋白質も重要な役割を果たすことがわかっている．RDはチロシナーゼおよび2種類のチロシナーゼ関連蛋白質の働きを抑制することにより，メラニン生成を抑制する．

そのメカニズムの詳細は不明ながらも以下のように考えられている．RDはメラニン生成の出発材料であるチロシンとその構造が類似しているため，本来はチロシンが結合するべきチロシナーゼの活性中心に結合する．その結果として，チロシナーゼに本来の反応基質であるチロシンが結合できなくなり，メラニン生成反応が進行せず，メラニンの生成が減少することになる．こういった酵素阻害様式を拮抗阻害という．拮抗阻害作用は，チロシンとRDの相対的な濃度によって決定されるので，RDの濃度が減少，つまり使用を中止すれば，その効果は消えるものと考えられる．また，脱色素斑部ではメラノサイトの減少が認められることから，メラノサイトへのなんらかの障害作用もあることが推測されている（図3〜5）．

Ⅲ．RD脱色素斑の臨床症状の特徴および前駆症状

①RDを含有する化粧品を使用後2カ月から3年経ち，不完全脱色素斑*が顔面，頸部，手背，腕に分布する．脱色素斑はまだらなことが多く，色素脱失の程度はさまざまである．色素脱失の程度が軽く，境界も不明瞭で一

見して目立たなくても，よくみると脱色素斑を生じていることもある．一方で境界明瞭な完全脱色素斑*に移行したと考えられる症例もみられる．なお，色素斑が完全か不完全かよく区別できない場合も，ダーモスコープで観察すると脱色素斑部において毛は色が付いている場合が多い．

②化粧品の塗布部位に痒みを伴う紅斑を認めることがある．炎症後に脱色素斑が生じる例や，脱色素斑と正常部の境界に炎症を伴う炎症型白斑*を呈する症例もある．まったく炎症を伴わない症例もある．炎症を伴う症例，伴わない症例ともにRDによるパッチテストが陽性の症例がある(図6)．なお炎症を伴う症例群のほうが，より高いパッチテスト陽性率を示す．

③RD含有化粧品の使用を中止後，6カ月くらいで色素再生を認める例が多い．完全脱色素斑から不完全脱色素斑を経て回復する場合や，毛包一致性の点状色素再生を認める場合がある．

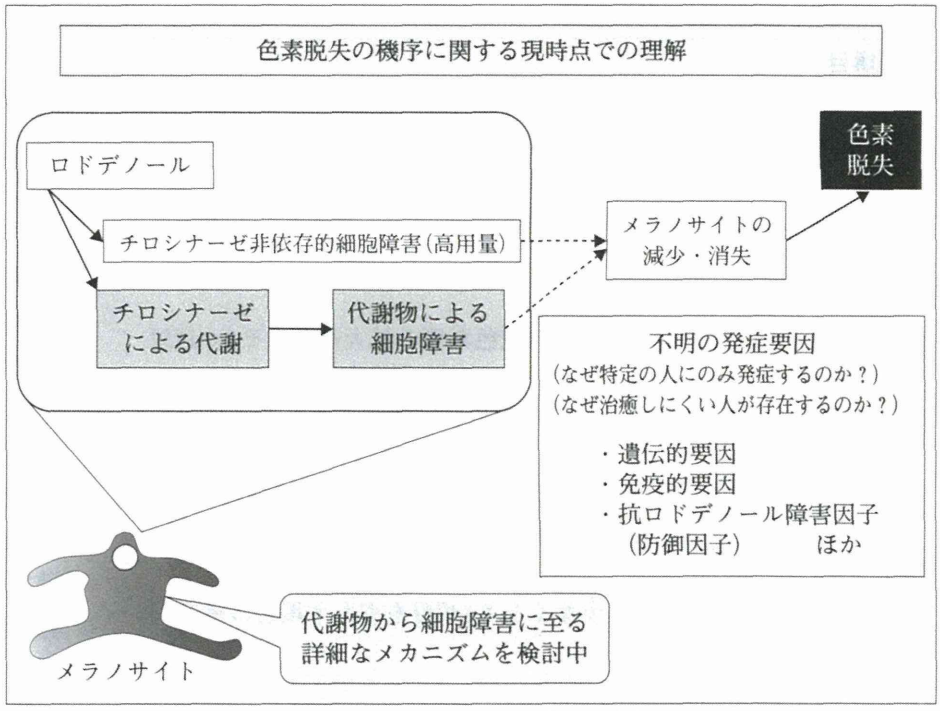


図5　RDによる色素脱失の機序に関する現時点での理解

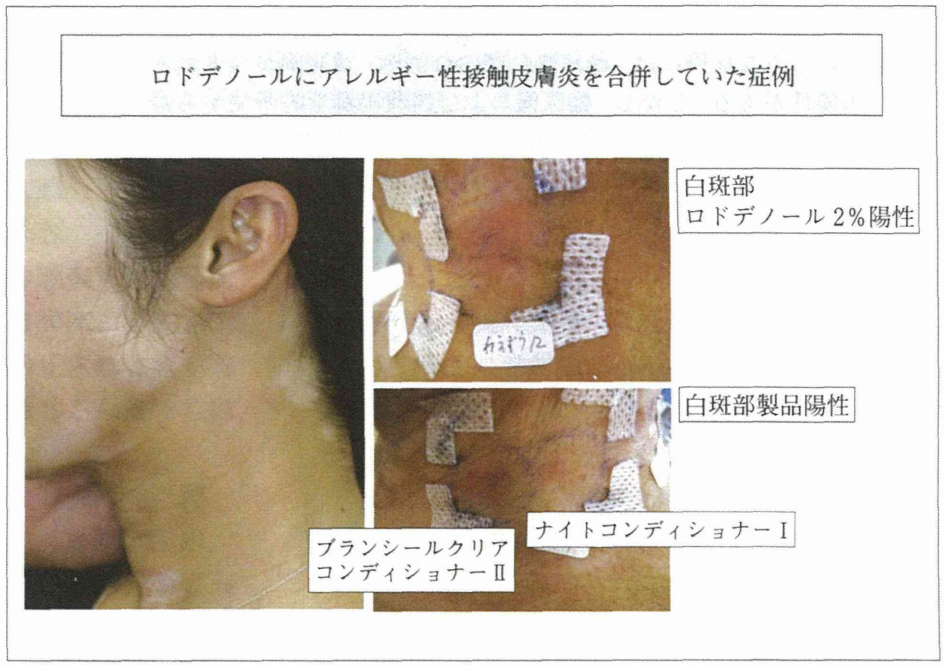


図6　RDにアレルギー性接触皮膚炎を合併していた症例の臨床像とパッチテスト陽性所見

④回復過程に色素増強(temporal excess) repigmentationを認める例がある．一過性の色素増強は軽快することが多い．

⑤大半が女性であるが，家族に勧められて使用した男性例もあった．

【用語の定義】

＊完全脱色素斑：ほぼ，あるいは完全にメラニン色素が欠如して，健常色を喪失し，白色調を呈する脱

表　RD誘発性脱素斑の診断基準

必須項目

1. ロドデノール含有化粧品を使用していた.
   注)患者申告 購入履歴, 回収記録を根拠に判断する.
2. ロドデノール含有化粧品を使用する前には脱色素斑がなく, 使用後, 使用した部位におおむね一致して生じた, 完全ないし不完全脱色素斑がある.

小項目

1. 使用中止により(必須項目 2. の)脱色素斑の拡大がおよそ1カ月以内に停止した.
2. 使用中止により(必須項目 2. の)脱色素斑の少なくとも一部に色素が再生した.
   注)写真や診療録, ダーモスコピー所見などの記録を参照し, 医師が視診により重症度判定基準を用いて判定する.

判定

・必須項目2項目と小項目の少なくとも1項目を満たす場合は確実例とする.
・必須項目2項目を満たすが, 小項目の1, 2ともに満たさない場合はその時点では疑い例とする.
・疑い例については引き続き注意深く色素再生の有無を経過観察することが望ましい.
   注)このような症例には, 尋常性白斑の合併例, 誘発例が含まれる可能性がある. しかし, 臨床像および病理組織学的所見から尋常性白斑とロドデノール誘発性脱色素斑を鑑別することは困難な場合があり, 診断には細心の注意が必要である.

色素斑.

＊不完全脱色素斑：メラニン色素が減少し, 健常色に比し白色調を呈するが, 健常色の完全喪失には至っていない脱色素斑. ただし, 両者の区別は視診で行うものとし, 混在していること, 連続していること, 時期によって変動することがある.

＊炎症型白斑：白斑の辺縁に紅斑や浸潤を伴う脱色素斑.

Ⅳ. 臨床分類

1. 完全脱色素斑優位型

完全脱色素斑のみ, もしくは完全脱色素斑優位(脱色素斑面積全体のうち6割以上が完全脱色素斑).

2. 完全・不完全脱色素斑混合型

完全脱色素斑と不完全脱色素斑優位がほぼ同じ割合で混在する.

3. 不完全脱色素斑優位型

不完全脱色素斑のみ, もしくは不完全脱色素斑優位(脱色素斑面積全体のうち6割以上が不完全脱色素斑).

Ⅴ. 病理組織像

生検組織の結果, 色素細胞が消失している症例, 色素細胞が減少している症例, 炎症細胞浸潤を伴っている症例や真皮浅層にメラノファージが散見されるだけの症例など, 臨床像と同じく病理組織像も多彩である. 尋常性白斑との鑑別について, ①毛嚢周囲に細胞浸潤がみられる, ②メラノファージが大多数の症例にみられる, の2点が尋常性白斑との区別の参考となる. メラノファージが認められないものは現時点では尋常性白斑の可能性が高いとの結論となっている. また, 尋常性白斑においては, 多くの場合, 完全脱色素斑部ではメラノサイトの完全な消失を認めるのに比して, 本疾患では臨床的に完全脱色素斑部でも, メラノサイトの減少はあっても完全に消失している症例は少数であり, 毛嚢部を含め標本上のいずれかの部位に残存を認める場合が多いことが明らかになっている(図7).

Ⅵ. 診　断

以上を踏まえて, RD脱色素斑の診断基準を作成した(表)[3].

Ⅶ. 鑑別診断

尋常性白斑との鑑別は尋常性白斑診療ガイドラインを参考に行う. 分節型は当該化粧品使用部位と一致しないので否定できる. 汎発型は区別がむずかしい場合がある. 脱色素斑の発症時期が当該化粧品の使用後であるか, 使用部位に一致しているか, 臨床的および病理組織学的に完全脱色素斑

であるか，甲状腺機能，膠原病，糖尿病，Addison病，脱毛の有無等も，必要に応じて確認し，除外する必要がある．

二次調査の結果，当該化粧品の中止により72％の患者で使用していた部位に色素の再生がみられている．したがって，経過観察により色素再生が認められれば，RD誘発性脱色素斑の可能性が高いと考えられる．

Ⅷ. 患者数・発生頻度

2014年11月28日現在，RDで脱色素斑を生じた症例は19,370名にのぼっており，　そのうち9,243名(47.7％)が完治・ほぼ回復したとカネボウ化粧品の調査で報告されている[9]．RD含有化粧品使用者が80万人と推定されているので，使用者の約2.4％が発症したことになる．

Ⅸ. パッチテスト陽性例の頻度

これまでに予備試験を含めて52施設199例のパッチテスト結果が収集されている．そのうち，48時間後のみの判定しか記載がなく，陽性の判断が困難であった14例を除く185例につき解析した．その結果，①2％RD白色ワセリン基剤陽性は全体の13.5％(25/185)，②炎症あり症例の陽性率は20.0％(20/100)，③炎症なし症例の陽性率は6.8％(5/74)，④炎症の有無が不明の症例での陽性率は0％(0/11)，⑤1週間後判定時に2％pet貼布部(健常皮膚部)に「白斑出現」

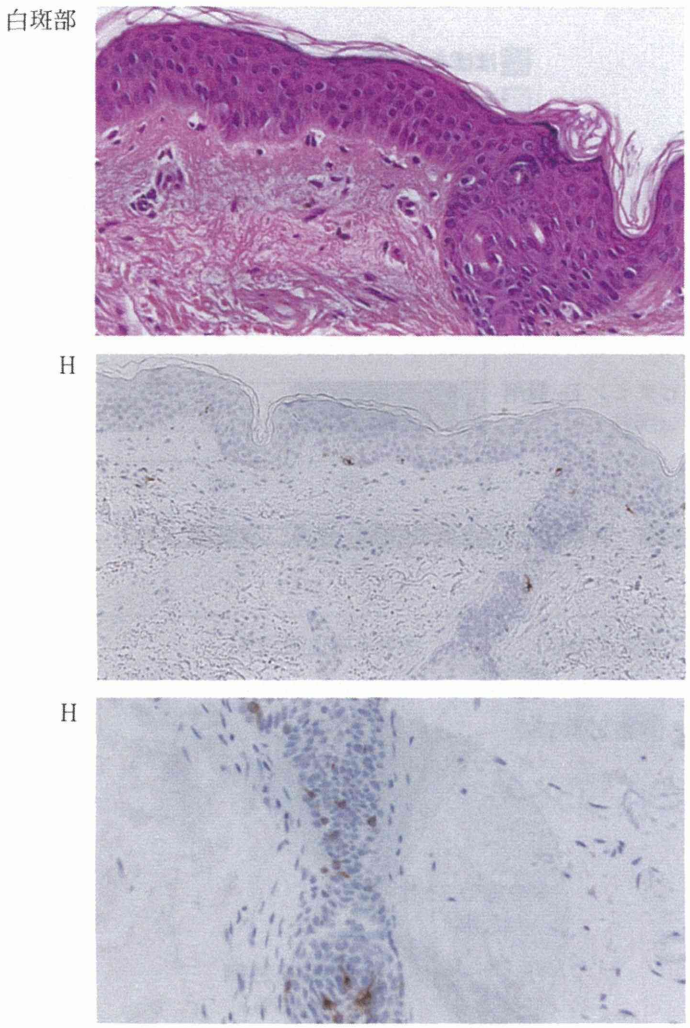


図7　RD誘発性脱色素斑症例の脱色素斑部の病理組織像

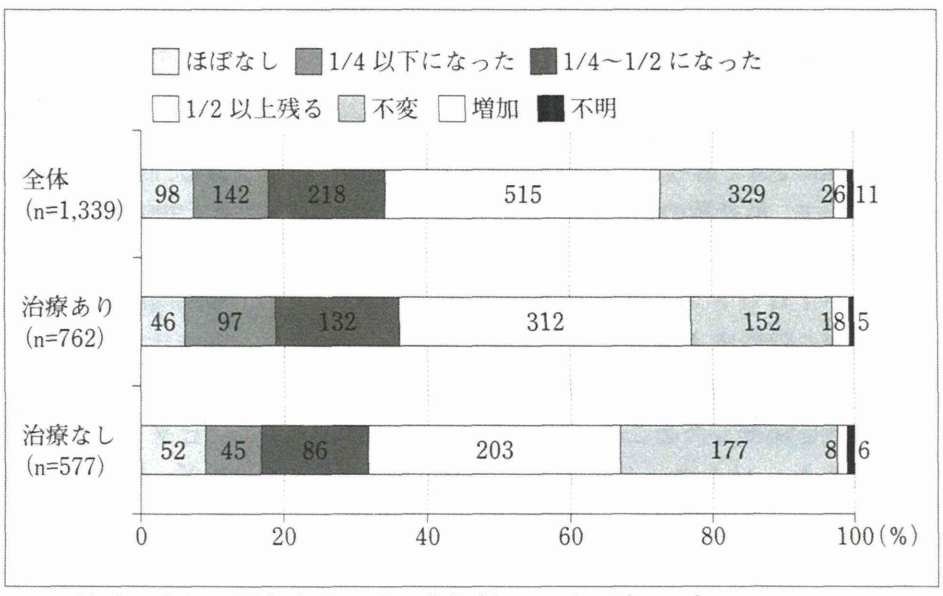


図8　治療の有無と脱色素斑面積の変化(全国二次調査より)

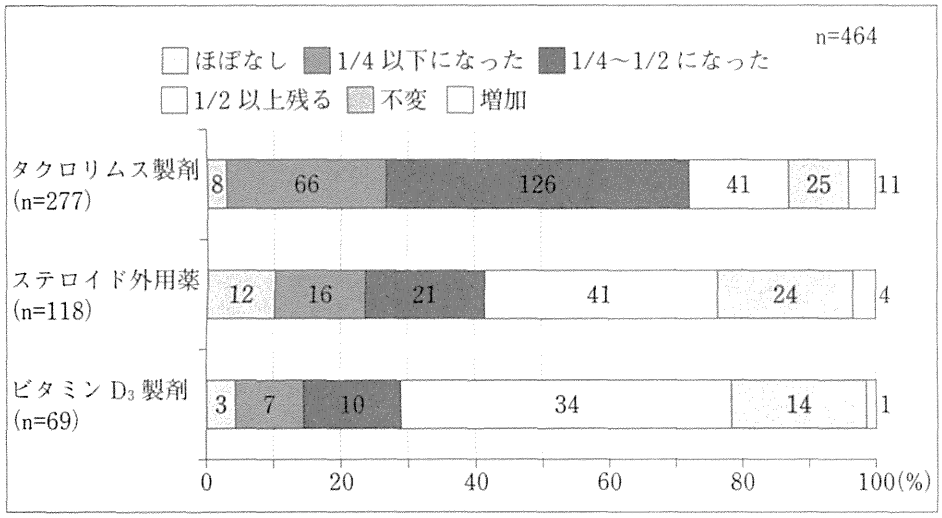


図9　外用薬と脱色素斑面積(全国二次調査より)

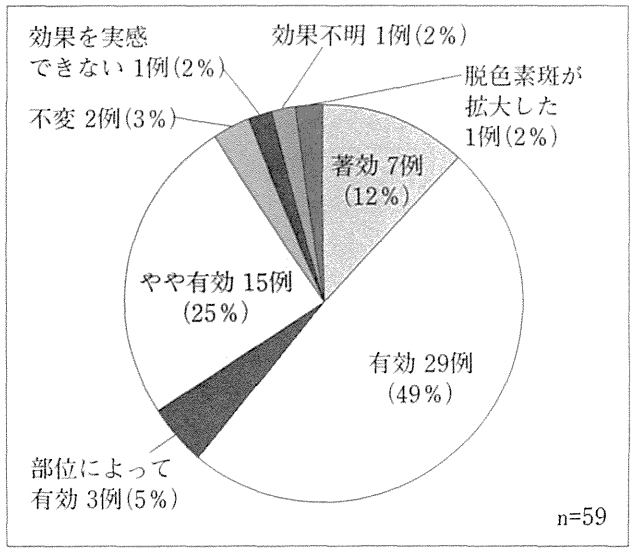


図10　紫外線治療の効果

と記載ある症例が1例，「うっすら白いか」と記載ある症例が1例であった．これら2例は別の施設からの報告で，集計数の約1%(2/199)になる．

2%RD白色ワセリン基剤を全国に配布する前に行ったパイロットスタディでは，5%RD白色ワセリン基剤の陽性率も検討した．73例に貼布し，2%が陰性であった54例のうち26例に5%RD白色ワセリン基剤を貼布したところ，4例(15.4%)に陽性反応を認めた．パイロットスタディーではRDの光線過敏についても検討し，52例に光パッチテストを施行した．その結果，UVA照射により反応が増強した症例が1例あった．

X. 予　後

2014年1月に行った全国二次調査では，「経過観察あり」と回答のあった1,399例中，7%は「脱色素斑がほぼなくなった」，11%は「1/4以下になった」，16%は「1/4～1/2になった」，38%が「1/2以上残る」，25%は「不変」，2%が「増加」，0.9%が「不明」，0.1%が「評価困難」であった(図8)．自主回収から半年後の調査であったため，中止して半年経過した患者さんが最多であったが，118例が，1年以上前に当該化粧品を中止しており，このうち6割以上は医療機関で経過観察中に脱色素斑面積が縮小傾向ありと回答している．全国二次調査時点では，まだ中止後1年を経過していない症例が多く，これからも引き続き経過観察をする必要がある．治療の有無で比較してみると，なんらかの治療を受けた方の77%が，また，治療せずに経過をみている方でも67%が脱色素斑面積の縮小傾向を示していた．

XI. 治療と経過

1. 治療の基本

まずは当該化粧品を中止したうえで，遮光をしっかり行い，経過観察をすることが第一選択である．前述の全国二次調査の結果，経過観察のあった1,399例中「治療あり」は57%，「治療なし」は43%であった．無治療で経過をみている症例でも67%が回復傾向を示し，なんらかの治療を受けている方では77%が回復傾向を示していた．

2. 治療の内容

ビタミンC，トラネキサム酸，ビタミンE，アレルギー薬などの内服治療と，タクロリムス軟膏，ステロイド外用薬，ビタミンD_3外用薬などによる外用治療，ならびに紫外線治療等が行われている．

3. 外用薬治療と経過

タクロリムス外用薬単独使用群，ステロイド外用薬単独使用群，ビタミンD_3外用薬単独使用群の3群で比較すると，タクロリムス軟膏単独使用群が，ほかの外用薬単独使用群や，治療なしと回答した群に比べて，脱色素斑面積の評価（ほぼなくなった；1/4以下になった；1/4～2/1になった；1/2以上残る；不変；増加）で，「半分以下に縮小している」と回答した割合が高く（**図9**），色素増強も含めた総合評価（治癒；かなり軽快；軽快；やや軽快；不変；増悪）でみると，ステロイド外用薬単独使用群で「軽快以上」の評価であった症例の割合が高くなっていた．ビタミンD_3外用薬の効果は，症例数も少なくはっきりした有効性は確認できていないが，タクロリムス軟膏やステロイド軟膏を用いにくい症例では試みてもよいと考えられている．

4. 紫外線治療と経過

「紫外線治療あり」と回答のあった75例に対して2014年5月に治療内容や効果を再度調査したところ（集計対象66例），効果について回答のあった60例中，著効からやや有効と回答したのは56例（84.8％）であった．化粧品中止の効果と判別がむずかしいという意見も複数あり，紫外線治療により1例は「脱色素斑面積が拡大した」，2例は「不変」，1例は「軽快しているが紫外線治療の効果であると実感できない」と合計4例（6.0％）が回答している．紫外線治療は，ほかの治療で軽快がみられない症例には試みてよい治療方法と思われる（**図10**）．

ただし，紫外線治療の効果はあったが「刺激が出現しやすく照射量を低めに設定した」，「脱色素斑周囲に色素増強をきたしたので中止した」という回答もあり，低容量の紫外線照射から始め，周囲の健常皮膚の遮光に十分注意して行うことが必要である．

5. 治療のまとめ

以上の全国二次調査の結果から，原因となった化粧品使用中止後一定の期間（6カ月程度）が経過しても脱色素斑の改善がみられない部位には，通常の尋常性白斑の治療が有効と思われる．なお，塗布部位や症状によっても治療法の選択は変わってくるので，経過観察以外に，これらの治療の選択は主治医の判断が尊重される．治療と経過についても，三次調査でさらに検討を行う予定である[7]．ヒトの皮膚モデルマウスにRDを外用したところ患者でみられた脱色素斑と同様な脱色素斑が生じることが明らかになった．

おわりに

現在までに，脱色素斑が改善している症例が多いが，一部では，難治の症例もある．RD誘発性脱色素斑の発症機序については，RDの代謝，作用など化学物質からの解明，なぜ一部の人にだけ，まだらに脱色素斑が生じたのかという個体側の要因等を解明すべきであるが，病態はまだ十分解明できていない．現在，ゲノム解析を含む研究が進んでおり，今後，さらに病態の解明がなされることと考える．

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JAPANESE DERMATOLOGICAL ASSOCIATION
THE JOURNAL OF DERMATOLOGY

doi: 10.1111/1346-8138.12744

Journal of Dermatology 2015; **42**: 113–128

COMMITTEE REPORT

Guide for medical professionals (i.e. dermatologists) for the management of Rhododenol-induced leukoderma

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ABSTRACT

Because some users develop depigmentation after the use of melanogenesis-inhibiting products containing the quasi-drug ingredient Rhododenol, Japanese Dermatological Association (JDA) established a Special Committee on the Safety of Cosmetics Containing Rhododenol on July 17, 2013 and management guide for dermatologists has been updated on the website in order to delineate the diagnostic criteria for Rhododenol-induced leukoderma and provides a broad guide for standard treatment based on current knowledge. This guide is produced on the basis of the guide (version 7) updated on June 20, 2014 in the website. Rhododenol-induced leukoderma refers to depigmentation of varying severity that develops after the use of cosmetics containing Rhododenol, mainly at the site of use. In most cases, repigmentation of part or all the affected area is evident after discontinuation. Histopathologically cellular infiltration around the hair follicles and melanophages are present in most cases. The number of melanocytes in the lesion is declined but not totally absent in most cases. Rhododenol itself is a good substrate for tyrosinase, resulting in the formation of Rhododenol metabolites (e.g., Rhododenol quinone). Melanocytes are damaged by Rhododenol metabolites during the subsequent metabolic process. The continued use of cosmetics containing Rhododenol thus induces tyrosinase activity-dependent cytotoxicity in melanocytes in the epidermis at application sites, resulting in decreasing the amount of melanin produced by melanocytes; the addition of some other factor to this process is believed to subsequently cause the decrease or disappearance of melanocytes themselves from the epidermis.

Key words: **cosmetics, leukoderma, Rhododenol, skin-lightening agent, ultraviolet light irradiation.**

INTRODUCTION

Because not a few users developed depigmentation after the use of melanogenesis-inhibiting products manufactured and sold by Kanebo Cosmetics (Tokyo, Japan), Lissage (Tokyo, Japan, merged into Kanebo Cosmetics Inc. as of January 1, 2014) and L'Equipe (Tokyo, Japan) that contain the quasi-drug ingredient Rhododenol (a brand name of rhododendrol, 4-[4-hydroxyphenyl]-2-butanol), a voluntary recall of cosmetics containing Rhododenol was launched on 4 July 2013.

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This is the secondary English version of the original Japanese manuscript for Guide for medical professionals (i.e. dermatologists) for the management of Rhododenol-induced leukoderma published in the Japanese Journal of Dermatology 124(3); 285–303, 2014, with some additional information from the "Guide for the dermatologists for managing the Rhododenol-induced leukoderma ver.7" appeared in the website of the Japanese Dermatological Association.

Received 6 November 2014; accepted 6 November 2014.

A large number of the patients have consulted dermatologists throughout Japan, but many issues regarding Rhododenol-induced leukoderma remain unclear, including the causal relationship between Rhododenol and clinical symptoms as well as its clinical forms, incidence, prognosis and pathogenesis. Thus, dermatologists are struggling to deal with these issues in clinical practice.

In accordance with its position of responsibility, the Japanese Dermatological Association (JDA) established a Special Committee on the Safety of Cosmetics Containing Rhododenol on 17 July 2013 in order to survey the actual situation of patients, provide correct information for medical professionals (i.e. dermatologists) and patients, elucidate the pathogenesis of this phenomenon, and urgently establish diagnostic and treatment methods; this committee has already initiated its activities.

First, information about the features of the cases collected so far including laboratory data were provided for doctors who are members of the JDA. Given the inadequacy of currently available clinical information, we are currently aggregating the cases in order to provide necessary and update information for use in clinical management. The guide herein only constitutes preliminary information, and it should not be regarded as drawing any conclusions.

This guide (version 7) was produced on 20 June 2014. In addition to data from the preliminary questionnaires sent by dermatologists to the Special Committee, information from emails and other sources, and survey results provided by Kanebo Cosmetics, this guide also includes the results of the nationwide secondary questionnaire. Moreover, it describes the currently emerging knowledge of the pathogenesis of this condition and provides new information on matters such as treatment policy. Thus, we hope it will be a useful reference for management.

STATUS OF THIS MANAGEMENT GUIDE

The Special Committee on the Safety of Cosmetics Containing Rhododenol, which was established by the JDA on 17 July 2013, immediately began deliberations involving its members and collaborating researchers in committee meetings and by discussions through emails. The resultant management guide delineates the diagnostic criteria for Rhododenol-induced leukoderma and provides a broad guide for standard treatment based on current knowledge.

DISCLAIMER

This management guide summarizes the opinions Special Committee members based on the data available at the time of writing; its content may be revised without warning in the future in accordance with new research findings. Doctors engaged in treatment may deviate from this management guide in accordance with the conditions of individual patients; in fact, such deviations may be preferable. Therefore, we are unable to accept any liability for negligence arising solely from the fact that doctors engaged in treatment have complied with this management guide; furthermore, any deviation from this management guide should not necessarily be regarded as negligence.

Q1. What symptoms have been reported?

A1. Disease concept: Rhododenol-induced leukoderma

What is Rhododenol-induced leukoderma?

Rhododenol-induced leukoderma refers to depigmentation of varying severity that develops after the use of cosmetics containing Rhododenol, mainly at the site of use. In most cases, repigmentation of part or all the affected area is evident after discontinuation.

Diagnostic criteria

Essential criteria

1. History of the use of cosmetics containing Rhododenol.

Note: This was determined on the basis of evidence from patient reports, purchase history and collection records.

2. No history of depigmentation prior to the use of cosmetics containing Rhododenol and the presence of complete or incomplete depigmentation that is mostly coincident with sites of use.

Minor criteria

1. Depigmented areas (item 2 of the essential criteria) stopped increasing in size within approximately 1 month of discontinuation.
2. Pigment in at least part of the depigmented areas (item 2 of the essential criteria) regenerated after discontinuation.

Note: This was determined on the basis of visual inspection by doctors using severity assessment criteria with reference to records including photographs, medical records and dermoscopic examination.

Reference criteria

1. Inflammatory symptoms such as erythema may be apparent prior to the appearance of depigmentation.
2. Depigmentation may not be of uniform severity and is often uneven with irregular margins.
3. It tends to occur if multiple cosmetics containing Rhododenol have been used together and at sites of repeated application.

Diagnoses by exclusion

Leukoderma due to the following must be excluded: Vogt–Koyanagi–Harada disease, Sutton nevus, infection-associated leukoderma (e.g. pityriasis versicolor, syphilis, leprosy and HIV), pityriasis simplex, leukoderma senilis, vitiligo vulgaris, postinflammatory depigmentation due to other causes, drug-induced melanoleukoderma, occupational leukoderma, piebaldism, Waardenburg syndrome and congenital pigmentary disorders such as tuberous sclerosis.

Assessment

Confirmed cases exhibit both items of the essential criteria and at least one minor criterion.

Patients who exhibit both items of the essential criteria but do not meet either items 1 or 2 of the minor criteria are regarded as suspected cases at that point.

Suspected cases should undergo continued careful follow up to watch for repigmentation.

Note: In rare cases, patients may be complicated with vitiligo vulgaris or have vitiligo vulgaris triggered by Rhododenol-induced leukoderma. It may be difficult to distinguish between vitiligo vulgaris and Rhododenol-induced leukoderma on the basis of clinical characteristics and histopathological findings. Thus, the diagnosis must be meticulous.

Specific example 1 (patients with prior vitiligo vulgaris and concomitant Rhododenol-induced leukoderma): Patients who exhibited depigmentation diagnosable as vitiligo vulgaris prior to the use of cosmetics containing Rhododenol, but in whom depigmentation appeared and spread mainly at locations where cosmetics containing Rhododenol had been used and repigmentation of these areas occurred when the use of these cosmetics was discontinued should be regarded as patients with vitiligo vulgaris complicated by Rhododenol-induced leukoderma.

Specific example 2 (patients with Rhododenol-induced leukoderma and concomitant vitiligo vulgaris): Patients who have developed depigmentation at locations where cosmetics containing Rhododenol have been used, and either these areas had stopped expanding after the use of these cosmetics was discontinued or the depigmentation had partially improved, but depigmentation had spread at locations where these cosmetics had not been used should be regarded as patients with Rhododenol-induced leukoderma complicated by vitiligo vulgaris.

The diagnosis of such patients must be based on the judgment of the individual attending physician in accordance with factors including the patient's clinical presentation, use of cosmetics concerned, timing of discontinuation and course of subsequent depigmentation.

Clinical classification

(1) Predominantly complete leukoderma.

Solely or predominantly complete leukoderma (i.e. complete leukoderma accounting for at least 60% of the total area of depigmentation).

(2) Mixed complete and incomplete leukoderma.

Mixed complete and incomplete leukoderma in approximately equal proportions.

(3) Predominantly incomplete leukoderma.

Solely or predominantly incomplete leukoderma (i.e. incomplete leukoderma accounting for at least 60% of the total area of depigmentation).

Characteristics of clinical and prodromal symptoms

1. Incomplete leukoderma distributed on the face, neck, backs of the hands, and forearms between 2 months and 3 years after the use of cosmetics containing Rhododenol. The depigmentation is mottled and varies in severity. It may be mild and with poorly demarcated margins, meaning it is not obvious at first observation but is discernible on close examination. However, this may progress to well-demarcated complete leukoderma in some patients. Even if it is difficult to clearly determine if pigmentation is complete or incomplete, dermoscopic examination can often reveal if the hairs in depigmented areas are colored.

2. Itchy erythema may be present in locations where these cosmetics have been applied. Some patients may develop depigmentation following inflammation, while others exhibit inflammatory vitiligo with inflammation at the boundaries between areas of depigmentation and healthy skin. Meanwhile, some patients exhibit no inflammation at all. Regardless of the development of inflammation, patients may react positively to Rhododenol in patch tests. However, patients having leukoderma associated with inflammation tend to have a higher positive rate on patch tests.

3. Repigmentation mostly occurs approximately 6 months after the use of cosmetics containing Rhododenol has been discontinued. Patients may recover from complete leukoderma via incomplete leukoderma, and follicular punctate repigmentation may also occur.

4. Temporary excess repigmentation may occur during the recovery process in some cases; such transient excess pigmentation is usually improved.

5. A large majority of patients are women, but some men have also developed this condition after using cosmetics containing Rhododenol on the advice of family members.

Definitions

1. Complete leukoderma: Whitish depigmentation with near complete or complete absence of melanin pigment and loss of normal color.

2. Incomplete leukoderma: Depigmentation with a decrease in melanin and a comparatively whitish appearance compared with normal color but not amounting to a total loss of normal color.

Note: these conditions are distinguished on the basis of visual examination and may be mixed, continuous or vary over time.

3. Inflammatory vitiligo: Depigmentation with erythema or infiltration along the rim of the vitiligo.

Histopathology

We are currently investigating the results of biopsies mainly from patients at institutions with which members of the Special Committee are affiliated. The histopathology is as diverse as the clinical profile, with melanocytes having disappeared in some patients and decreased in others, and some patients exhibiting inflammatory cell infiltration and others with only scattered melanophages in the superficial dermis. The following points may be useful for distinguishing from vitiligo vulgaris: (i) cellular infiltration around the hair follicles; and (ii) melanophages are present in almost all patients. At this point, if melanophages are not evident, it can be surmised that there is a high possibility the patient has vitiligo vulgaris. Most patients with vitiligo vulgaris completely lose all melanocytes in areas of complete leukoderma, whereas in this particular condition, this was the case for only a few patients in areas of clinical complete leukoderma, even if the number of melanocytes in those locations had declined; their presence was observed in some parts of specimens, including hair follicles.

Prognosis

The secondary questionnaire carried out in January 2014 indicated that 1339 cases were "under observation". Of these,

depigmentation had virtually disappeared in 7%, decreased to less than one-quarter of its initial area in 11%, decreased to between one-quarter and one-half of its initial size in 16%, remained more than half its initial size in 38%, remained unchanged in 25% and increased in size in 2% (n = 26); the outcome was unknown in 0.9% and 0.1% (n = 1) could not be evaluated.

Q2. Which cosmetics are covered by this guide?

A2. Melanogenesis-inhibiting products containing the quasi-drug ingredient Rhododenol (4-[4-hydroxyphenyl]-2-butanol). It is suspected that some people who have used cosmetics for inhibiting melanogenesis may develop an overinhibitory reaction or inflammation.
The products concerned are melanogenesis inhibitors manufactured and sold by Kanebo Cosmetics, Lissage and L'Equipe that contain the quasi-drug ingredient Rhododenol. A list of product names is available on the following websites:
Ministry of Health, Labor and Welfare website: http://www.mhlw.go.jp/stf/houdou/2r98520000035xv0.html.
Kanebo Cosmetics website: http://www.kanebo-cosmetics.jp/information/#products_name.

Q3. What sort of substance is Rhododenol (4-(4-hydroxyphenyl)-2-butanol)?

A3. (1) Which products contain Rhododenol?
Rhododenol is a substance that inhibits melanogenesis that was developed in-house by Kanebo Cosmetics. As a substance with a "whitening effect", it has been incorporated into numerous products produced by Kanebo Cosmetics that promise to whiten skin. As it was developed in-house and patented by Kanebo Cosmetics, it is not contained in cosmetic products produced by other manufacturers.

(2) How was it developed?
According to Kanebo Cosmetics, they focused on a substance called 4-(4-hydroxyphenyl)-2-butanol after screening several plant-derived natural substances for melanogenesis-inhibiting effects. Subsequent in-depth research revealed Rhododenol is an extremely potent melanogenesis inhibitor. It was approved in 2008 by the Ministry of Health, Labor and Welfare for its efficacy in preventing skin blotches and freckles by inhibiting melanogenesis.

(3) How does Rhododenol work to whiten skin?
Blotches develop on the skin as a result of excessive melanin deposition. Melanin is synthesized in melanocytes within the skin by an enzyme called tyrosinase, which plays the most important role in melanogenesis. The starting point for the series of reactions whereby melanin is formed is the oxidation of tyrosine by tyrosinase, which is the rate-limiting enzyme for the melanin-synthesis process; if this reaction does not occur, then no melanin is produced at all. Rhododenol binds to the active site of tyrosinase, where ordinary tyrosine should bind, because the chemical structure of Rhododenol is similar to tyrosine. This prevents tyrosine, the substrate for the reaction, from binding to tyrosinase, reducing melanin production. Rhododenol itself is a good substrate for tyrosinase, resulting in the formation of Rhododenol metabolites (e.g. rhododendrol quinone). It is also believed that melanocytes are damaged by rhododendrol quinone and further metabolites during the subsequent metabolic process. The continued use of cosmetics containing Rhododenol thus induces tyrosinase activity-dependent cytotoxicity in melanocytes in the epidermis at application sites, resulting in the formation of large quantities of the metabolites and decreasing the amount of melanin produced by melanocytes; the addition of some other factor to this process is believed to subsequently cause the decrease or disappearance of melanocytes themselves from the epidermis. A mild decline in the capacity for melanogenesis acts to whiten the skin, but a pronounced decrease in melanocytes results in depigmentation. These findings corroborate the previous report of the Special Committee, specifically histopathological tests of affected sites showing a decrease in melanocytes in areas of depigmentation, leading to the conjecture that some sort of melanocyte-damaging action is involved.
According to a study by Kanebo Cosmetics, depigmentation has occurred in approximately 2% of people who have used cosmetics containing Rhododenol. Why some people develop depigmentation whereas others do not remains unclear; we are currently investigating the reason for this.

Q4. How many people are affected?

A4. Kanebo Cosmetics is currently visiting all customers who have reported problems to them and confirming their symptoms. A media announcement by the company on 9 June 2014 states that the confirmed number of people affected stood at 14 612 as of 31 May 2014.
An estimated 800 000 people have used cosmetics containing Rhododenol, meaning that approximately 2% of users have developed depigmentation.
According to the 9 June announcement, of the 14 612 affected individuals, 1613 had developed "obvious leukoderma across a wide area of the face, hands, or elsewhere", and 4649 had either "leukoderma in at least three places", "leukoderma at least 5 cm in size" or "obvious leukoderma on the face", while 8350 exhibited symptoms milder than this. Among all patients, 4297 (29.4%) have recovered either completely (according to either a doctor's diagnosis or the patient's own report) or almost completely. Kanebo Cosmetics has collated cases of patients whose symptoms could be compared between the first, second and subsequent visits. They reported that symptoms improved between the first and second visits in 784 of 942 patients (83.2%) with "obvious leukoderma across a wide area of the face, hands, or elsewhere", and in 1848 of 2002 people (79.7%) with either "leukoderma in at least three places", "leukoderma at least 5 cm in size" or "obvious leukoderma on the face".
According to Kanebo Cosmetics, almost 100% of products containing Rhododenol have been recovered in the voluntary recall.

The JDA Special Committee on the Safety of Cosmetics containing Rhododenol had received primary questionnaires referring to 1338 cases as of 7 September 2013. As such, we would like to thank you for your cooperation.
We have collated the results of secondary questionnaires from institutions with which Special Committee members and collaborators are affiliated with, and we have formulated diagnostic guidelines and a severity-grading sheet based on current knowledge about the pathogenesis of this condition. We hope it will prove useful in clinical management.
It is important that severity is evaluated over time. We request that you keep accurate and detailed medical records as well as photographs, if possible (with the patient's consent).

Q5. A patient has asked me to provide a medical certificate. What should I do?

A5. At this point, a medical certificate is unnecessary for the voluntary product recall or to make a report to Kanebo Cosmetics. Should Kanebo Cosmetics or another organization require a medical certificate in the future, please describe patients as either confirmed or suspected cases of Rhododenol-induced leukoderma with reference to the diagnostic criteria proposed by the Special Committee in section A1 above.
If a patient needs to take time off work for a patch test or any other reason, they may need to submit a medical certificate to their employer. Please provide such medical certificates on your own authority as a doctor. Before a definitive diagnosis has been reached, the reason may be described as "suspected contact dermatitis" or "contact dermatitis" if this has been confirmed by a patch test.

Q6. How can Rhododenol-induced leukoderma be distinguished from vitiligo vulgaris?

A6. Please refer to the vitiligo vulgaris guidelines. Segmental vitiligo can be excluded, as it does not develop bilaterally and co-localize with the site where the cosmetics concerned have been used. It may be difficult to distinguish it from generalized vitiligo. Check whether the depigmentation developed following the use of the cosmetics concerned, whether it occurred in the same areas where they were used, whether it constitutes complete leukoderma clinically and histologically, and if required, investigate whether thyroid dysfunction, connective tissue diseases, diabetes, Addison's disease or hair loss is present, because it may be necessary to exclude these.
According to the results of the secondary questionnaire, pigmentation recovered at the site of use in 72% of patients after they discontinued using the cosmetics concerned. If repigmentation is observed over time, this indicates a high probability of Rhododenol-induced leukoderma.
See the diagnostic criteria given in section A1 above.
Some specialists consider that the possibility of progression to vitiligo vulgaris because of the use of the cosmetics concerned cannot be ruled out. At present, this possibility can be neither confirmed nor denied, because vitiligo vulgaris of generalized form is an autoimmune disease and the mechanism whereby this autoimmunity arises is unknown. When such patients are encountered, it is envisaged that a thorough examination will enable some of these cases to be distinguished from vitiligo vulgaris, while others must be treated as indeterminate. This is a question for future study.

Q7. Is not Rhododenol-induced leukoderma a type of drug-induced photosensitivity?

A7. Some patients taking thiazide antihypertensives have been diagnosed with drug-induced melanoleukoderma, but they exhibited no changes in clinical symptoms despite being instructed to discontinue taking these medications; they were later found to have been using the cosmetics concerned. It normally takes approximately 6 months after discontinuing medication for the melanoleukoderma rash to improve; therefore, careful follow up is important. As it is clinically difficult to differentiate these diseases, and it is also difficult to verify their causal relationship, it is vital to check what medications patients are taking. If one of their medications is a potential cause of melanoleukoderma (Table 1), they should preferably be instructed to discontinue it or to switch to a different drug.

Table 1. *Drugs that may induce melanoleukoderma*

Thiazide antidiuretics	Hydrochlorothiazide, chlorothiazide
Other antidiuretics	Meticrane
Antibiotics	Tetracycline, fleroxacin, griseofulvin
Muscle relaxants	Afloqualone
Non-steroidal anti-inflammatories	Tiaprofenic acid
Beta-blockers	Pindolol

Q8. Should patients be asked about their history of phenol and phenol compound use in order to distinguish Rhododenol-induced leukoderma from occupational one?

A8. Always ask patients about their occupation and history of exposure. The occurrence of similar depigmentation has been reported in employees of factories handling phenol and phenol compounds as well as hydroquinone; these chemicals are found in adhesives, inks, varnishes, various types of synthetic resin-modifying agents, raw materials for perfumes, insecticides, bactericide, rubber antioxidants, raw materials for vinyl chloride stabilizers, surfactants and other antioxidants, and oil additives.

Q9. Are the patch test and photopatch test necessary?

A9–1. To date, we have been sent the results of patch tests from 199 individuals from 52 institutions, including preliminary tests. After excluding 14 patients for whom only evaluations after 48 h were recorded, meaning that a positive determination could not be made, we analyzed the results of 185 cases.
(1) Of the patients, 13.5% (25/185) reacted positively to 2% Rhododenol in a white petrolatum base.
(2) The positive rate for patients with inflammation was 20.0% (20/100).

(3) The positive rate for patients without inflammation was 6.8% (5/74).
(4) The positive rate for patients for whom the presence of inflammation was unknown was 0% (0/11).
(5) One patient was recorded as "displaying leukoderma" and another as "possibly faintly white" in areas to which 2% Rhododenol in white petrolatum had been applied (to healthy skin) on assessment after 1 week. These two patients were reported by different institutions and accounted for approximately 1% of the total (2/199).

A9–2
(1) We investigated the positive rate from a pilot study of 5% Rhododenol in a white petrolatum base performed before the 2% Rhododenol in a white petrolatum base was distributed nationwide. This was applied to 73 patients; 26 of 54 patients who were negative to 2% Rhododenol were tested for 5% Rhododenol and four (15.4%, 4/26) exhibited a positive reaction.
(2) In the pilot study, we also investigated the photosensitivity of Rhododenol and performed photopatch tests on 52 patients. Only one patient exhibited a new or increased positive reaction after ultraviolet A irradiation; this patient did not constitute a confirmed case of photoallergy.
Patch tests should be performed in the future when possible. We are able to send out 2% Rhododenol in a white petrolatum base. However, please be aware that supplies are limited.
Caution: Before performing this test, patients should be informed that depigmentation may occur at the site of the patch test and their consent should be obtained beforehand.

Notes

Application site: Even if only a few applications are performed, they should be made to an unobtrusive site such as the back rather than the outside of the upper arm. If the test is performed in summer, it should be done in a cool environment or while the patient is hospitalized to avoid sweating. Performing the patch test once the weather has cooled should also be considered.
Timing of assessment: In addition to usual examinations at 48 h, 72 h and 1 week, the application site should also be examined until 1–2 months later to determine if depigmentation has occurred. See Q10 for information on how to obtain the test material for the patch test.

Q10. How can I obtain the test material for the patch test?

A10. We are distributing 2% Rhododenol in a white petrolatum base as a test material for diagnostic patch tests. Institutions that would like to be sent this test material should contact us at the following address. Please be aware that supplies are limited: JDA Administration Team, 4-1-4 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. Email: gakkai@dermatol.or.jp; Fax: 03-3812-6790.

Q11. Is a skin biopsy required?

A11. The diversity of clinical symptoms is becoming clearer as the cases of Rhododenol-induced leukoderma will be accumulated. Biopsies that have already been performed show a decline in the number of melanocytes. Some patients who exhibit severe inflammation exhibited a lichenoid reaction. Performing a biopsy may help elucidate unclarified points such as whether or not symptoms vary depending on the stage of the disease and if there is any recovery of depigmentation; in addition, it may provide valuable information for the management of individual patients. Nevertheless, patients must be informed that a biopsy is an invasive procedure and does not always lead to a definitive diagnosis. Therefore, informed consent must be obtained before a biopsy is performed. The choice of harvesting site and immobilization method should be determined by the attending physician's discretion.

Note: Depending on the features of the case concerned, potential harvesting sites may include areas of depigmentation and erythema, healthy areas and areas of pigment deposition. A biopsy should be performed when you consider it essential for diagnosis. As they are covered by health insurance, they are basically performed by the attending physician's discretion.
If undifferentiated cells in hair follicles (i.e. melanocyte stem cells) are maintained and melanocytes in the epidermis, which are differentiated to some extent, have been affected, the color may recover at the area consistent with pores and surrounding the depigmentation. Therefore, some specialists believe biopsies of the depigmented area should include hair follicles. The number of melanocytes can be investigated by hematoxylin–eosin staining of paraffin-embedded slices, which can be combined with immunostaining such as Melan-A.
The Special Committee is undertaking histopathological analysis using special staining. Any useful information gained from this will be published; this will be followed by further studies by individual medical institutions.

Q12. Are blood tests required?

A12. If blood tests are required to distinguish Rhododenol-induced leukoderma from other disorders that cause depigmentation, they should be performed at the attending physician's discretion. At present, there have been a few cases of concomitant thyroid disorder. There is a tendency for patients to test positively for autoantibodies (including antithyroglobulin antibody and anti-thyroid peroxidase antibody), which often exhibit abnormal levels in autoimmune thyroid disorders, even though thyroid dysfunction may not be evident. Concordant with the primary questionnaire, blood tests should be performed at the attending physician's discretion if they are required for diagnosis. Please freeze and store any leftover sera. Should future studies identify any diagnostically valuable autoantibodies or other factors, we will publish this information.

Q13. Will the depigmentation recover?

A13. The nationwide secondary questionnaire carried out in January 2014 showed that 1339 cases were "under observation". Of these, depigmentation had virtually disappeared in 7%, decreased to less than one-quarter of its initial area in

11%, decreased to between one-quarter and one-half of its initial area in 16%, remained more than half its initial size in 38%, was unchanged in 25%, had increased in size in 2% (n = 26), outcome was unknown in 0.9% and could not be evaluated in 0.1% (n = 1).

As this survey was performed 6 months after the media story broke, most patients had discontinued the use of cosmetics containing Rhododenol 6 months prior; however, 118 had already stopped using these cosmetics at least 1 year prior, and in 60% of these patients, the area of depigmentation was reportedly contracting during follow up at medical institutions. At present, most patients have discontinued use less than 1 year ago. Therefore, continued follow up is necessary. A comparison of whether or not patients have undergone treatment showed that the area of depigmentation is decreasing in 77% of the patients who have received some sort of treatment but in 67% of those who are simply being followed up without treatment.

Q14. Should the use of skin-whitening cosmetics be prohibited in future?

A14. As the pathogenesis of this condition remains unexplained, no convincing evidence is currently available. Patients should be informed that it is impossible to completely rule out the risk of the same symptoms appearing from other skin whiteners and their use left to their own discretion. Individual patients should be instructed what to do according to the condition of their own blemishes and depigmentation.

Q15. Are other skin-whitening products safe?

A15. There have been reports of a few cases of the occurrence of similar depigmentation after the use of other skin-whitening cosmetics. As there is currently no available information on the safety of skin-whitening cosmetics with the same mechanism of action, it is impossible to state if they are safe or dangerous. When examining patients, it is always necessary to ask whether they have a history of using other skin-whitening products as well as cosmetics containing Rhododenol. Regardless of the product, resultant skin problems should always be treated individually by a dermatologist. The Ministry of Health, Labor and Welfare has also requested cosmetics companies to investigate whether any cases of similar symptoms of depigmentation due to skin-whitening cosmetics have occurred. See A26.

Q16. How should I treat patients who ask for any remaining blemishes to be treated with hydroquinone?

A16. There have been multiple reports of the simultaneous appearance of symptoms of depigmentation and chloasma, although the causal relationship is presently unknown. Hydroquinone has been used in some of these cases. There have been no reports of depigmentation when hydroquinone is used at a concentration of approximately 5%. Hydroquinone exhibits weaker cytotoxicity than hydroquinone monobenzylether, and its action is reversible. However, if users are exposed to strong ultraviolet light during the day, their blemishes may actually darken. If they use hydroquinone in the morning, they are advised to also use a product containing a sunblock of at least skin protection factor 30 and apply hydroquinone only once in the evening if they are exposed to strong ultraviolet light over long periods or are unable to protect themselves against ultraviolet light. Hydroquinone is a highly effective compound but must be used correctly. Doctors must carefully check that patients are using it correctly; and if patients are unable to use it properly, they should be instructed not to apply it. A study of 52 patients at 13 institutions who simultaneously applied Rhododenol and hydroquinone found that 11 reacted positively to a patch test with 2% Rhododenol in a white petrolatum base but all 11 reacted negatively to 1% hydroquinone in a white petrolatum base. Thus, it appears that no cross-reaction occurs.

Q17. Should patients be instructed to protect themselves from light?

A17. As the pathogenesis of this condition remains unexplained, there is currently no convincing evidence that photoprotection is necessary. There are reports of patients who developing Rhododenol-induced leukoderma when they used the cosmetics concerned after sunburn overseas or noticed it after becoming sunburned, suggesting that there may be some connections among onset, the use of the cosmetics concerned and exposure to ultraviolet light. Although it is unclear how long the effect of these cosmetics persists after their use has been discontinued, in most cases, melanocytes do not disappear entirely even though their number has declined; this suggests that the ability to produce melanin is preserved by the remaining melanocytes. Some patients have also been observed to suffer from transient pigment intensification during repigmentation. In the opinion of specialists, although the color will eventually match, it may be better to use photoprotection to encourage cosmetically satisfactory pigment regeneration without an obvious contrast between depigmented and repigmented areas. As the facial area is vulnerable to photoaging and prone to the development of blemishes, it may be a good idea to advise patients to avoid sunburn. In addition, patients can be advised to use sunscreen while checking that they are not developing contact dermatitis or photocontact dermatitis against sunscreens. It may be safest to perform a patch test or a test application twice daily for 1 week on an area approximately 2 cm in diameter exposed to ultraviolet light.

Q18. What treatments are effective?

A18. The only first-choice treatment is to discontinue the use of the cosmetics concerned, employ thorough photoprotection and monitor the patient's condition without treatment. However, the national secondary questionnaire in January 2014 revealed that 57% of the 1341 patients being followed up were receiving treatment while 43% were not. Improvement was evident in 67% of those who did not undergo treatment compared to 77% of those who did. The types of treatment include oral medication including vitamin C, tranexamic acid, vitamin E and anti-allergy drugs; topical medications including tacrolimus

ointment, topical steroids and topical vitamin D3; and ultraviolet light therapy. The efficacy of topical therapy was compared among patient groups comprising monotherapy with tacrolimus, steroids or vitamin D3. A greater proportion of patients receiving topical tacrolimus monotherapy reported that the depigmented area had decreased to less than half its initial area (assessed as either virtually disappeared, decreased to less than one-quarter its initial area size, decreased to between one-quarter and one-half its initial size, still more than half its initial size, no change or increased in size) compared with those receiving monotherapy with other topical agents and those not undergoing treatment.

Regarding overall assessment (i.e. recovered, greatly improved, improved, somewhat improved, no change or worse) including hyperpigmentation, a greater proportion of patients undergoing monotherapy with steroids was evaluated as "improved" or better.

In May 2014, a reassessment of the type of treatment used and its effectiveness in 59 of the 74 patients reported to be undergoing ultraviolet light treatment showed that 54 of 59 patients who responded regarding its effectiveness stated that it was from somewhat to very effective. Although we have received several opinions that its effect is difficult to distinguish from that of discontinuing the use of the cosmetics concerned, only one patient reported that the area of depigmentation spread as a result of ultraviolet light treatment, two reported no change, and one reported that although it improved, it was not due to the therapy; these findings suggest that this therapy may be worth trying for patients who do not exhibit any improvement. Although some effect was observed, great care is required, because there are also reports that irritation tends to occur, prompting the exposure to be set to a low dose; furthermore, there are reports of treatment discontinuation after hyperpigmentation developed around the area of depigmentation. As some patients improved without treatment, it is difficult to precisely differentiate between the effects of discontinuing cosmetic use and topical agents or ultraviolet light treatment on areas of Rhododenol-induced depigmentation. However, the results of the secondary questionnaire suggest that the routine treatment for vitiligo vulgaris may be effective to some extent. The type of treatment method will also vary depending on the area of application and symptoms as well as the question of whether to use any sort of treatment other than monitoring the patient's course. Ultimately, the attending physician's discretion should be respected.

Q19. Is phototherapy effective?

A19. In May 2014, a reassessment of the types of treatment used and their effectiveness in 59 of the 74 patients who were reported to be undergoing phototherapy (i.e. ultraviolet light treatment) in the nationwide secondary questionnaire revealed that most were being treated with excimer light, narrowband ultraviolet B, VTRAC, or a combination of these once or twice weekly, or depending on the patient's schedule. Moreover, 54 of 59 patients who responded regarding its effectiveness stated that it was from somewhat to very effective. Ten had finished treatment, because the depigmentation was no longer obvious. Four patients discontinued phototherapy because of hyperpigmentation of the irradiated area around the area of depigmentation. This hyperpigmentation was sufficiently severe such that it obviously contrasted with the depigmentation. Although we have received several comments that the effect of ultraviolet light treatment is difficult to distinguish from that of discontinuing cosmetic use, only one patient reported that the area of depigmentation spread as a result of ultraviolet light treatment, two reported no change, and one reported that although it improved, they did not feel it was due to the effect of ultraviolet light. These results suggest that this treatment method may be worth attempting in patients who do not exhibit repigmentation over the long term. However, great care is required, as there have also been reports of a tendency for irritation to occur, prompting the exposure to be set to a low dose. Furthermore, there have been reports in which the treatment was discontinued when hyperpigmentation developed around the area of depigmentation.

Q20. Is topical treatment effective?

A20. As described in A18, the nationwide secondary questionnaire carried out in January 2014 showed that improvement was evident in 77% of those who were undergoing treatment as well as in 67% of those who had been monitored without treatment after discontinuing the use of the cosmetics concerned. The first-choice treatment is to stop using the cosmetics concerned, employ thorough photoprotection and follow up without treatment. However, in severe cases, no repigmentation may be apparent in some patients who are only monitored without treatment; alternatively, if recovery is slow, topical treatment may tend to increase the rate of improvement. Topical agents may be effective for the treatment of patients with delayed repigmentation or severe inflammatory cell infiltration on histological examinations, erythema or suspected contact hypersensitivity to the cosmetics concerned. As described in A18, in the secondary questionnaire, a greater proportion of patients treated with topical tacrolimus reported that the area of depigmentation had decreased, while a greater proportion of patients treated with topical steroids were evaluated as having improved in the overall assessment, including hyperpigmentation.

When using a topical agent, proceed cautiously at your discretion as a specialist dermatologist by applying it to part of the depigmented area and observing whether there is a greater effect there than in the untreated area as well as monitoring for side-effects. Meanwhile, tacrolimus ointment should be applied once in the evening, and patients should be instructed to use sunscreen during the day. Few patients have been treated with topical vitamin D3 ointment; although its effectiveness has not been clearly established, no patient's condition has been reported to have worsened.

Q21. Is vitamin D3 ointment effective?

A21. Few patients have been treated with this agent; although its effectiveness has not been clearly established, no patient's condition has been reported to have worsened as a result. It may be worth trying in patients who have difficulty using tacrolimus or steroid ointment.

Q22. What kind of patient information is required?

A22. Many issues regarding Rhododenol-induced leukoderma remain unclear, including the causal relationship between Rhododenol and clinical symptoms as well as its clinical forms, incidence, prognosis and pathogenesis. Resolving these issues will require gathering information from numerous clinical case studies. Furthermore, the JDA is conducting epidemiological surveys mainly via its Special Committee. First, it is recommended that the dermatologists record the patient's past history and clinical findings according to the primary questionnaire (that can be downloaded from the JDA website). This questionnaire also includes sections for information on tests, treatment, and the patient's course; it is designed so as not to interfere with patient examinations. The deadline for returning the secondary questionnaire passed on 31 January 2014, but a third questionnaire is being planned to be sent out in approximately 1 year. To track the severity of individual cases over time, we would like to request diligence when recording information including the location of depigmentation and its clinical classification in medical records as well as the provision of photographs whenever possible. Please download and use the severity assessment sheet for tracking the severity of depigmentation over time that we have developed.
See Q26 for patients with depigmentation suspected to be due to cosmetics other than Rhododenol.

Q23. What is the JDA planning to do in future?

A23. As an immediate measure for investigating the cause of Rhododenol-induced leukoderma, the JDA set up its Special Committee on the Safety of Cosmetics Containing Rhododenol on 7 July 2013 and appointed Professor Kayoko Matsunaga of the Department of Dermatology of Fujita Health University School of Medicine as its chair. The Special Committee held its first meeting on 19 July 2013 and embarked on activities including survey studies, elucidating the pathogenesis of this condition, diagnosis and treatment, and providing information. A case review meeting was held on 11 August 2013. The second Special Committee meeting was held on 7 September 2013, resulting in the production of version 5 of the management guide. The Special Committee met for the third time on 2 November 2013 and continued its discussions toward the formulation of this management guide. It also implemented a secondary questionnaire for institutions with which members of the Special Committee and collaborating researchers are affiliated; version 6 of this management guide was produced on 12 December 2013 on the basis of the collated results. The fourth, fifth and sixth Special Committee meetings were held on 10 January, 14 March and 31 May 2014, respectively; during these meetings, the committee gathered and considered information from studies designed to help elucidate the pathogenesis of Rhododenol-induced leukoderma. The results of the nationwide secondary questionnaire implemented in January had been collated at this point and were incorporated into version 7 of this management guide, which has been published and uploaded. Further information divided into information for doctors as well as patients and the general public will continue to be published on the JDA website. Version 6 of the management guide has been published in the *Japanese Journal of Dermatology*, and will later be published in the JDA's English-language journal, the *Journal of Dermatology*. The date of publication will be announced on this website once it has been decided.

Q24. Are medical costs covered by health insurance?

A24. Contact dermatitis and depigmentation caused by cosmetics are skin disorders that are covered by health insurance in Japan. Please leave any issues such as corporate compensation for copayments to the negotiations between patients and their employers. There is no need for doctors to get involved.

Q25. Please explain what is known about why this depigmentation occurs?

A25. Rhododenol is believed to be associated with the development of depigmentation. The evidence for this is as follows:
(1) According to a press release by Kanebo Cosmetics, dated 24 November 2013, depigmentation has been confirmed in 16 864 individuals who had used cosmetics containing Rhododenol. A questionnaire of doctors revealed over 1200 patients with evident depigmentation.
(2) Repigmentation of depigmented areas occurs after discontinuing the use of cosmetics containing Rhododenol, and most patients are recovering.
(3) According to a survey by Kanebo Cosmetics, although numerical data have been produced on the basis of inaccurate information and are thus inaccurate themselves, the incidence among patients tended to increase in the order of those who used only toner containing Rhododenol; both toner and lotion; and toner, lotion and cream.
(4) In some patients, depigmentation occurred after itchiness or erythema developed after using cosmetics containing Rhododenol; some of these patients had positive patch test results with the cosmetics concerned and Rhododenol.
(5) It is now known that Rhododenol is metabolized into a cytotoxic substance by tyrosinase in melanocytes (see Q3).
(6) The number of melanocytes in the epidermis decreases in areas of depigmentation.
(7) It was found that the model mice with mimic human skin developed leukoderma similar to Rhododenol-induced leukoderma after the application of Rhododenol.
However, it has not been fully clarified why some people develop leukoderma and some do not. At present, the reason is under investigation by the Special Committee members. The new findings will be informed when we obtain the reliable information in the future.