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GUIDELINE

Guidelines for the diagnosis and treatment of vitiligo in Japan

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ABSTRACT

Vitiligo is an acquired pigment disorder in which depigmented macules result from the loss of melanocytes from the involved regions of skin and hair. The color dissimilarity on the cosmetically sensitive regions frequently induces quality of life impairment and high willingness to pay for treatment in patients with vitiligo. The Vitiligo Japanese Task Force was organized to overcome this situation and to cooperate with the Vitiligo Global Issues Consensus Conference. This guideline for the diagnosis and treatment of vitiligo in Japan is proposed to improve the circumstances of Japanese individuals with vitiligo. Its contents include information regarding the diagnosis, pathogenesis, evaluation of disease severity and effectiveness of treatment, and evidence-based recommendations for the treatment of vitiligo. The therapeutic algorithm based on the proposed recommendation is designed to cure and improve the affected lesions and quality of life of individuals with vitiligo.

Key words: **algorithm, diagnosis, guideline, phototherapy, vitamin D_3 analogs, vitiligo.**

INTRODUCTION

Vitiligo is the most common acquired depigmented disorder characterized by the progressive loss of melanocytes. It is mainly classified into segmental and non-segmental vitiligo. The color dissimilarity of the cosmetically sensitive regions is associated with significant burden, as reflected by the quality of life (QOL) impairment and high willingness to pay for treatment, especially in women.[1] A strategic guideline for the treatment of vitiligo with evidence-based evaluation has not been established.[2] Recently, novel therapies such as topical application of vitamin D_3 analogs and narrowband ultraviolet B (NB-UVB) have become more common. Thus, a guideline for the diagnosis and treatment of vitiligo in Japan would be indispensable for Japanese dermatologists making decisions regarding the management of vitiligo.

BACKGROUND OF THE GUIDELINE

The Vitiligo Japanese Task Force (VJTF) was organized for the proposition of the guideline for the diagnosis and the treatment of vitiligo in cooperation with the Japanese Dermatology Association (JDA) in October 2009.[3] The guideline was published in the Japanese published work in July 2012.[4] This English version was designed as a brief review to announce its content to scientists, physicians and dermatologists world-

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wide. The members of the VJTF participated in the Vitiligo Global Issues Consensus Conference to cooperate with an update of the uniform concept of vitiligo and its treatment strategy.

LIMITATION OF THE GUIDELINE

This guideline was proposed following an evaluation of the established and published evidence. A forthcoming update is essential, as novel treatment may overcome current management recommendation and unexpected adverse reactions may occur in the future. The VJTF states no guarantee of protection for physicians and dermatologists against any conflict, although physicians and dermatologists insist that they refer to and follow this guideline. Dermatologists are free to manage vitiligo with strategies that are not recommended in this guideline. Therefore, the VJTF states no guarantee of protection for patients and their agents against any conflict, although patients and their agents insist that physicians and dermatologists do not refer to and do not follow this guideline. This guideline does not represent law or legal advice.

EVIDENCE LEVEL AND RECOMMENDATION

Each evidence level and recommendation was decided as described in the instructions of the guidelines for management of skin cancer (Table 1).[5]

Table 1. Criteria for levels of evidence and grades of recommendation

A. Levels of evidence
I. Systematic review or meta-analyses
II. One or more randomized controlled trial(s)
III. Controlled study without randomization
IV. Analytical epidemiological studies (cohort studies and/or case–control studies)
V. Descriptive studies (case reports and/or case accumulation studies)
VI. Expert committee reports or opinions from each specialist
B. Grades of recommendation
A. Strongly recommended to perform (there should be at least one level I or II study that indicates effectiveness)
B. Recommended to perform (there should be at least one level II study of low quality, level III of good of quality or level IV of extremely good quality that indicates effectiveness)
C1. Can be considered for use, but there is insufficient evidence (level III–IV evidence of low quality, plural level V of good quality or level IV approved by the committee)
C2. Not recommended for use because there is no evidence (there is no evidence that indicates effectiveness or there is evidence that indicates no effects)
D. Recommended to avoid (there is good evidence that indicates no effect or harmful effects)

This table was cited from Saida *et al.*[5] with modification.

EPIDEMIOLOGY

We classified congenital and acquired depigmented disorders as shown in Figures 1 and 2, and sent a questionnaire to 262 major hospitals including all universities and medical colleges in Japan. Their replies are summarized in Figure 3. The number of patients with congenital depigmented disorders diagnosed at their first medical examination were 1748 of 912 986, and 6359 patients had acquired depigmented disorders.[3] This response demonstrated that vitiligo accounted for approximately 60% of all depigmented disorders.[1] An epidemiological survey conducted by the JDA found that patients with vitiligo comprised 1134 (the 18th most prevalent disorder in the dermatological field in Japan) of 67 488 persons who had received their first medical examination during the predetermined days in each season.[6]

CLASSIFICATION AND PATHOGENESIS OF VITILIGO

Vitiligo is a common acquired depigmented disorder, with a prevalence of approximately 0.5–1.0% in most populations.[7,8] The segmental and non-segmental forms are believed to be caused by different pathogenic mechanisms (Table 2). Genetic and environmental factors are involved in the occurrence of non-segmental vitiligo. The presence of familial vitiligo in 20–30% of vitiligo cases suggests genetic susceptibility to this disorder.[9–11] Vitiligo patients show a strong epidemiological association with several other autoimmune diseases, particularly autoimmune thyroid disease, type 1 diabetes mellitus and pernicious anemia. Blood serum examinations in patients with vitiligo show higher percentage of positive autoantibodies such as anti-thyroglobulin and anti-peroxidase antibodies. These indicate that vitiligo is mainly caused by the autoimmune loss of melanocytes in the involved areas.

With a genome-wide association study, Spritz and colleagues showed that the *NALP1* region was associated with the risk of vitiligo and several epidemiologically vitiligo-associated autoimmune and autoinflammatory diseases in Caucasians.[12] Subsequent genome-wide association studies and meta-analyses have identified multiple loci. The susceptible genes are classified into autoantigens expressing in the melanocytes, innate immunity, acquired immunity, and other function and miscellaneous.

The involvement of humoral immunity in vitiligo has been demonstrated by the presence of autoantibodies that react to a variety of melanocyte-expressed proteins such as tyrosinase, tyrosinase-related protein 1 and tyrosinase-related protein 2.[13,14] These autoantibodies induce damage to melanocytes via complement-dependent cytotoxicity and/or antibody-dependent cellular cytotoxicity. The contribution of cell-mediated immunity has been shown by the presence of human leukocyte antigen A (HLA-A)*0201 restricted, melanocyte-specific $CD8^+$ T lymphocytes in peripheral blood cells[15] and the infiltration of $CD8^+$ effector lymphocytes in the dermis. Autoimmunity is believed to be the primary mechanism of vitiligo pathogenesis. Another hypothesis includes epidermal oxidative stress.[16,17] The genesis of segmental vitiligo has not been elu-

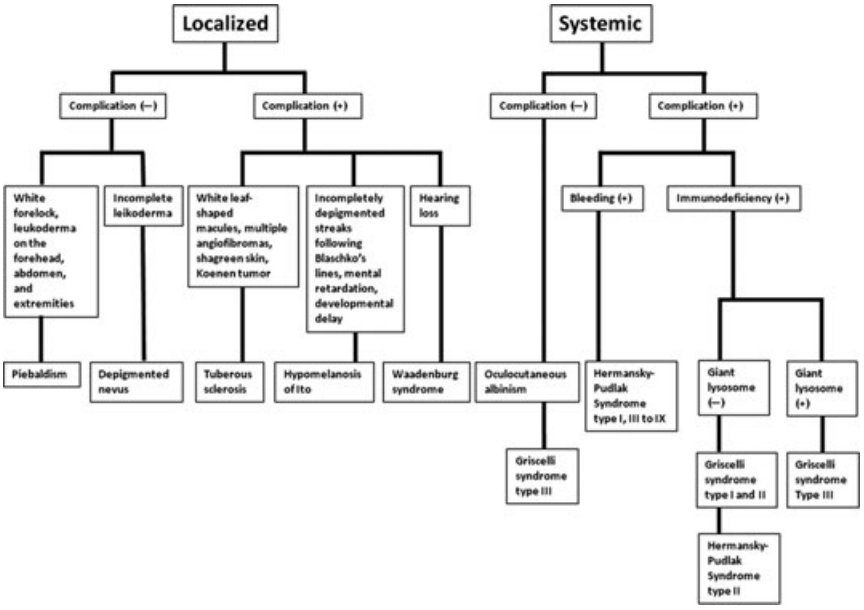

Figure 1. Classification of the congenital depigmented disorders of localized leukoderma and systemic albinism.

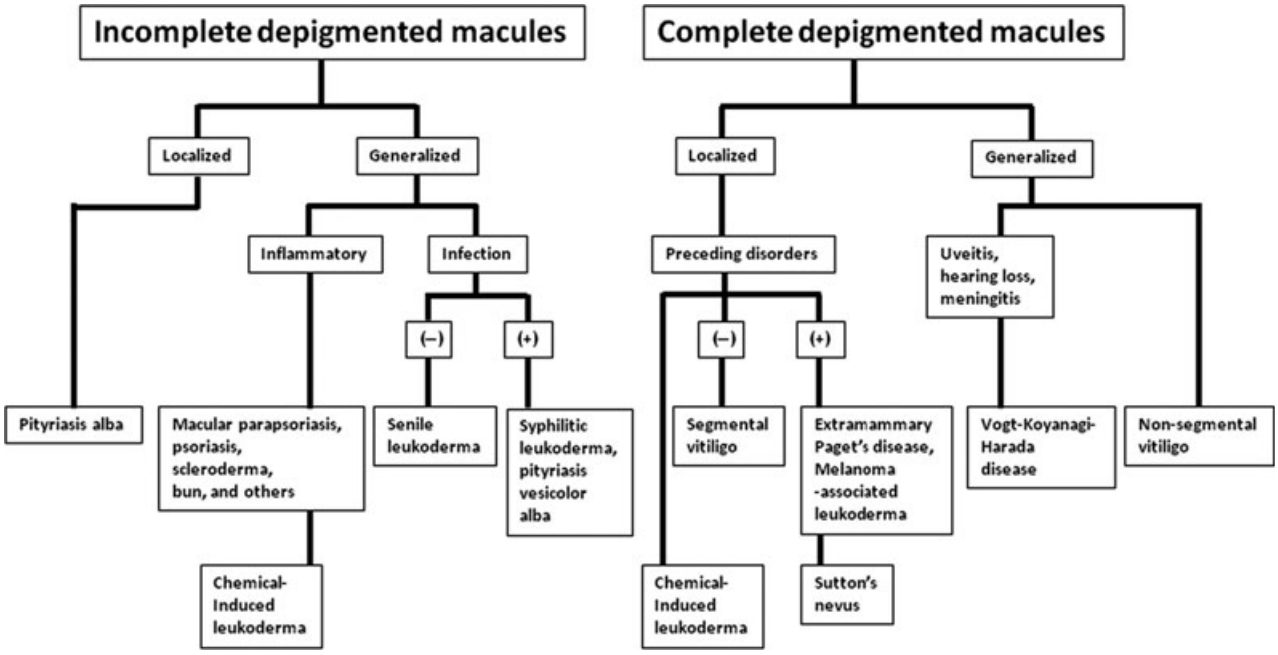

Figure 2. Classification of acquired incomplete and complete depigmented disorders.

cidated completely, despite the demonstration of elevated neuropeptide Y levels in the affected lesions.[18,19]

DIFFERENTIAL DIAGNOSIS

Vogt–Koyanagi–Harada disease

Vogt–Koyanagi–Harada (VKH) disease is a systemic disorder that affects the eyes, meninges, ears, skin and hair.[20] It is characterized by depigmentation of the affected tissues showing vitiligo, poliosis, and the sunset-glow fundus of the eyes in the late stage of the disease.[20] VKH is strongly believed to be caused by autoimmunity against melanocytes and melanin-producing cells.[20] In VKH, tyrosinase and gp100 (PMEL17) peptide-specific T-helper type 1 lymphocytes mediate an inflammatory response via producing regulated and normal T-cell expressed and secreted (RANTES),

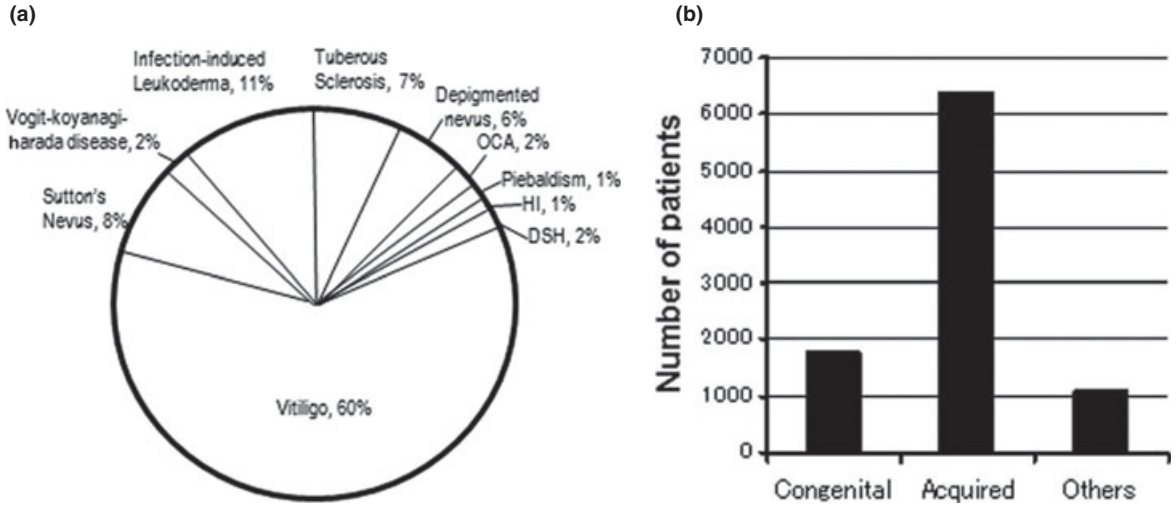

Figure 3. (a,b) Frequency of congenital and acquired depigmented disorders in Japan. The number of the patients at the first medical examination in 2009 was 912 986 in 262 major hospitals, including all universities and medical colleges. The patients with congenital depigmented disorders numbered 1748, and the patients with acquired depigmented disorders numbered 6359. DSH, dyschromatosis symmetrica hereditaria; HI, hypomelanosis of Ito; OCA, oculocutaneous albinism.

Table 2. Classification of vitiligo

1. Non-segmental vitiligo
This form includes mucosal, acrofacial, generalized and universal types, and some of focal type
2. Segmental vitiligo
This form includes some focal and mucosal types of vitiligo
3. Mixed vitiligo

chemokine (C-C motif) ligand 5 (CCR5) and interferon-γ (IFN-γ).

Sutton's phenomenon and Sutton's nevus

Sutton's phenomenon (halo phenomenon or leukoderma acquisitum centrifugum) is defined as the development of a halo of hypomelanosis around a central pigmented nevus, malignant melanoma or others. Sutton's nevus (halo nevus) is a specific halo around the nevus. Halo phenomenon/nevus is associated with the immunological response to the cells of the central nevi or tumors, namely, nevus or melanoma cells.

Infectious disorders

Acquired incomplete hypopigmented macules may be caused by various infectious disorders. Pityriasis versicolor, a fungal (*Malassezia furfur*) infectious disease, is manifested by discoloration (pityriasis versicolor nigra or pityriasis versicolor alba). Pityriasis versicolor alba is associated with incomplete transfer of melanosomes from melanocytes to keratinocytes[21] and inhibition of tyrosinase activity via C_9 and C_{11} dicarboxylic acids produced by *Pityrosporum* spp.[22] Syphilitic leukoderma, a distinctive feature of secondary syphilis, is characterized by rice-sized to nail-sized, small, obscurely demarcated, incompletely hypopigmented macules caused by decreased production of melanin granules.[23] Leukoderma can be seen in individuals infected by *Mycobacterium leprae* Hansen or HIV.

Pityriasis alba (pityriasis simplex facial)

Pityriasis alba is commonly present in children with atopic dermatitis and xerotic dermatitis. It may be confused by tinea corporis.

Senile leukoderma

Senile leukoderma is a feature of aging. It is caused by a decreased number of melanocytes and the subsequent reduction of melanin granules.

TREATMENT FOR VITILIGO

Current treatment for vitiligo in Japan

The replies to the questionnaire of the treatment of vitiligo from 262 major hospitals are summarized in Figure 4. Topical steroids, topical vitamin D_3 analogs and topical tacrolimus have been applied in almost all hospitals (~90%) and approximately 70% of institutes. Phototherapies are prevalent and are an evidence-based, highly effective treatment. They include not only traditional psoralen plus ultraviolet A therapy (PUVA) and broadband (BB)-UVB therapies but also developing NB-UVB and 308-nm excimer light/laser therapies. The efficacy of the combined treatments for vitiligo has been reported by many institutes. Camouflaging has been used for severe and stable vitiligo in approximately 90% of institutes. Topical bleaching agents for stable and treatment-resistant vitiligo are rarely applied in Japan, although this therapy is common in Europe and the USA.

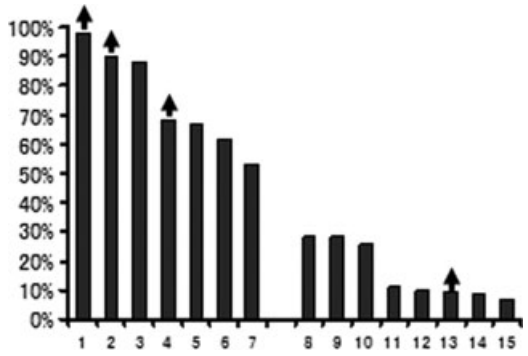

Figure 4. Situation of vitiligo treatment in 2010 in Japan. The percentages are based on the replies from 262 major hospitals, including all universities and medical colleges in Japan. (1) Topical corticosteroids; (2) camouflage; (3) topical vitamin D_3 analogs; (4) topical tacrolimus; (5) observation without any treatment; (6) narrowband ultraviolet B (NB-UVB) therapy;(7) topical psoralen and ultraviolet A (PUVA) therapy; (8) oral corticosteroids; (9) epidermal grafting; (10) mini-grafting; (11) topical bleaching agents; (12) 308-nm excimer laser/light therapy; (13) broadband (BB)-UVB therapy; and (14) abrasion. Treatments with increasing frequency of application include topical corticosteroids, camouflage, topical tacrolimus and 308-nm excimer laser/light therapy (arrows).

Evaluation of severity and treatment effectiveness in vitiligo

It is crucial to evaluate the severity of vitiligo and the efficiency of treatment. It should be discussed in global vitiligo task forces to provide uniform recommendations. Herein, we propose our theoretical explanation.

Evaluation of vitiligo severity. We proposed a classification system of vitiligo severity based on the JDA classification of atopic dermatitis severity:[24] mild, vitiligo covering less than 10% of the body surface area (BSA); moderate, vitiligo covering between 10% and 30% of the BSA; and severe, vitiligo covering more than 30% of the BSA.

Hoverer, QOL is superior to BSA. The patients with QOL impairment should be classified as those with the severe form. For example, vitiligo present on cosmetically sensitive regions with QOL impairment are classified as the severe form.[1]

Problem. This classification scheme is convenient, but it is unknown whether it is accepted by the societies for pigment cell research. It is difficult to apply this classification for evaluating the efficacy of the treatment.

Method for evaluating vitiligo severity. The Vitiligo Area Scoring Index (VASI) is recommended for the assessment of the affected surface area and the degree of depigmentation.[25] The evaluation should be performed on each area of the scalp, trunk, upper extremities and lower extremities.

Method for assessing progression and efficacy of the treatment of vitiligo. Progression and efficacy of the treatment of vitiligo can be evaluated with the VASI score. Follow-up assessments are recommended at 3 and/or 6 months after starting vitiligo treatment.

Problem. The VASI score is somewhat complicated, however, it is likely acceptable for the worldwide societies for pigment cell research. It is useful to apply the VASI score for the assessment of treatment efficacy.

Table 3. Summary of recommendations

Topical corticosteroids: A or B
Topical corticosteroids are effective for vitiligo
Topical vitamin D_3 analogs: C1–C2
Combination therapy with topical vitamin D_3 analogs and phototherapy (PUVA or NB-UVB) may be effective for vitiligo, although topical vitamin D_3 analogs alone are less efficient
Topical tacrolimus: B
Topical tacrolimus may be effective for vitiligo, although the safety of its continual use has not been established. Its effectiveness should be assessed 3 or 4 months after the initial use
Phototherapy with PUVA: B
PUVA therapy is effective for vitiligo
Phototherapy with NB-UVB: B
NB-UVB therapy is effective for adult vitiligo and is the first-line in phototherapy, as it is more effective than PUVA therapy. NB-UVB therapy is covered by Japanese public health insurance
Phototherapy with 308-nm excimer laser/light: C1
308-nm excimer laser/light therapy can be applied for vitiligo lesions in which repigmentation are expected. The features of this treatment should fully be addressed
Oral corticosteroids: C1
Oral corticosteroids can be administrated for progressing vitiligo
Immunosuppressive agents: ?
It is impossible to decide the grade of recommendation for immunosuppressive agents for the treatment of vitiligo, as only a treatment description was present[2]
Grafting and surgical treatments: A–C1
Grafting and surgical treatments should only be performed for stable and treatment-resistant vitiligo on cosmetically sensitive regions. Stability refers to no change of the affected lesions for at least more than 1 year
Camouflage: C1
Camouflage is valuable for improving QOL. Camouflage cannot cure vitiligo. Japanese health insurance does not cover camouflage

NB-UVB, narrowband ultraviolet B; PUVA, psoralen plus ultraviolet A therapy; QOL, quality of life.

Clinical questions

The briefs are summarized in Table 3.

Topical corticosteroids. Clinical question 1: Are topical corticosteroids effective for vitiligo? Recommendation: Topical corticosteroids are effective for vitiligo. Grade of recommendation: A or B.

Application of topical corticosteroids is the most prevalent treatment for vitiligo. It should be a first-line therapy for mild

or moderate vitiligo present on 10–20% of the BSA. As shown in Figure 4, almost all of the institutes use topical corticosteroids on the affected lesions. Topical application of class 2 (very strong) corticosteroids is effective, with over 75% repigmentation of localized vitiligo in 56% of cases.[26] Similarly, class 3 (strong) corticosteroid treatment is effective in 55% of cases.[26] In patients aged 15 years or below, it is suggested that class 4 (medium) corticosteroids should be applied to vitiligo lesions once a day for 4 months. In patients aged 16 years or above, it is recommended that class 2 (very strong) or class 3 (strong) corticosteroids be applied to vitiligo lesions for 4–6 months. Adverse reactions such as skin atrophy can occur due to long-term application of topical corticosteroids. No repigmentation after 2 months of topical corticosteroid treatment indicates the necessity to shift to second-line or other therapies. Repigmentation with topical corticosteroid treatment occurs in less than 20% of patients with non-segmental vitiligo.[27] Topical application of corticosteroids is not the first-line treatment of non-segmental vitiligo in adults, as phototherapy with NB-UVB is the first-line treatment.

The grade of recommendation for segmental vitiligo is A. The grade of recommendation for non-segmental vitiligo is B.

Topical vitamin D_3 analogs. Clinical question 2: Are topical vitamin D_3 analogs effective for vitiligo? Recommendation: Combined therapy with topical vitamin D_3 analogs and phototherapy (PUVA or NB-UVB) may be effective for vitiligo, although topical vitamin D_3 analogs alone are less efficient. Grade of recommendation: C1–C2.

Topical vitamin D_3 analogs are used for the treatment of vitiligo in approximately 90% of the institutes in Japan, although Japanese public health insurance does not cover this therapy. Recent reports suggest the possibility of the effectiveness of vitamin D_3 analogs.[28–30]

It has been discussed whether topical application of calcipotriol is effective for vitiligo, as the outcomes are controversial. The dissimilar results may be caused by the different reactivity of the lesions it is applied to, especially between sun-exposed and non-sun-exposed lesions. In Japan, it is forbidden to use calcipotriol on the face. The efficiency of tacalcitol hydrate and maxacalcitol for vitiligo has been reported, but they did not achieve sufficient evidence levels. At this point, a clear divergence of views emerges in the treatment of vitiligo with topical vitamin D_3 analogs.

The grade of recommendation for the treatment of vitiligo with topical vitamin D_3 analogs alone is C2. The grade of recommendation for the treatment of vitiligo with the combined therapy with topical vitamin D_3 analogs and phototherapy (PUVA or NB-UVB) is C1. Ermis *et al.*[30] showed that combination was more effective in their randomized trial. However, the examined number of the cases was not sufficient to enable an accurate evaluation. The divergent result was recently reported.

Topical tacrolimus. Clinical question 3: Is topical tacrolimus effective for vitiligo? Recommendation: Topical tacrolimus may be effective for vitiligo, although the safety of continual use has not been established. Its effectiveness should be assessed 3 or 4 months after initial use. Grade of recommendation: B.

Topical tacrolimus ointment is applied for vitiligo in approximately 70% of the institutes in Japan. Tacrolimus is the only topical calcineurin inhibitor that can be used in Japan, however, it is covered only for atopic dermatitis and not for vitiligo treatment by Japanese public health insurance. The efficiency of topical tacrolimus has been reported repeatedly over the latest decade. Once or twice daily application is effective for vitiligo. Twice daily treatment induced excellent repigmentation compared with no treatment in the same patients.[31] Hartmann *et al.*[32] reported that occlusive application enhanced the effectiveness of tacrolimus ointment in patients with vitiligo.

The grade of recommendation for the treatment of vitiligo with topical tacrolimus ointment is B. Combination therapy with topical tacrolimus and phototherapy has been examined in at least one placebo-controlled prospective trial. Although this combination therapy was reported to be effective for vitiligo, a long-term evaluation is necessary to address the recurrence of vitiligo and the unexpected carcinogenic effects. The combination therapy is currently contraindicated in Japan.

Phototherapy with PUVA. Clinical question 4: Is PUVA therapy effective for vitiligo? Recommendation: PUVA therapy is effective for vitiligo. Grade of recommendation: B.

Psoralen plus UV-A therapy has been used to radiate vitiligo lesions for half a century. In 1996, the American Academy of Dermatology published the guideline of care for vitiligo.[33] PUVA has been applied more frequently after being recommended as the treatment for vitiligo,[33] although its efficacy and recurrence rates are somewhat controversial. In 2002, Kwok *et al.*[34] retrospectively evaluated the efficacy of PUVA therapy for vitiligo. They demonstrated that complete repigmentation was achieved in eight of 97 patients radiated by PUVA and that moderate repigmentation occurred in 59 of 97 patients.[34] They discussed the necessity of informed consent for recurrence, as they showed frequent re-depigmentation rates 1 year after PUVA therapy in 57 patients.[34] In Japan, PUVA therapy has been used for the treatment of vitiligo.

The grade of recommendation for the treatment of vitiligo with PUVA is B. Recent studies suggest that NB-UVB therapy is superior to PUVA therapy, with higher efficacy and lower recurrence of vitiligo and the occurrence of adverse reactions. NB-UVB therapy is more prevalent than PUVA therapy in Japan. Excess photo-radiation in PUVA therapy may induce phototoxic reactions and skin cancer. A subsequent guideline should include a consensus decision to limit the total sum and number of sessions of PUVA therapy.

Phototherapy with NB-UVB. Clinical question 5: Is NB-UVB therapy effective for vitiligo? Recommendation: NB-UVB therapy is effective for adult vitiligo and is the first-line phototherapy, as it is more effective than PUVA therapy. NB-UVB therapy is covered by Japanese public health insurance. Grade of recommendation: B.

Narrowband UV-B represents a symbol of a specific UVB wave, 311 ± 2 nm. NB-UVB therapy was initially used for the treatment of psoriasis in the 1980s, primarily in Europe. NB-UVB was subsequently applied for the treatment of vitiligo in the 1990s.[35–37] Four randomized, controlled trials using NB-UVB for vitiligo treatment have been reported.[25,35,38,39] Hamzavi *et al.*[25] performed a controlled study of 22 vitiligo patients that received NB-UVB therapy thrice weekly on one side and no treatment on the other side for 6 months, and demonstrated statistically significant repigmentation on the NB-UVB-radiated side ($P < 0.001$). However, the efficacy of repigmentation was diverse in the affected regions.[25] The affected lesions on the dorsa of hands and feet were less responsive to NB-UVB than the lesions on the trunk and extremities.[25] A placebo-controlled, double-blind study of 56 non-segmental vitiligo patients demonstrated that: (i) the color match of the repigmented skin was excellent in all patients in the NB-UVB group but in only 11 (44%) of those in the PUVA group ($P < 0.001$); (ii) that the improvement in the BSA affected by vitiligo was greater with NB-UVB therapy than with PUVA therapy in patients who completed 48 sessions ($P = 0.007$); and (iii) that the superiority of NB-UVB tended to be maintained 12 months after the cessation of therapy.[26] A study of 281 vitiligo patients reported that the treatment of vitiligo patients with UV-B radiation is as efficient as treatment with topical PUVA, and has fewer adverse reactions.[35]

The guideline for the diagnosis and management of vitiligo in the UK proposed that safety limits for NB-UVB for the treatment of vitiligo are more stringent than those applied to psoriasis, with an arbitrary limit of 200 treatments for skin types I–III.[39] This limit could be higher for skin types IV–VI at the discretion of the clinician and with the consent of the patient.[39]

Njoo *et al.*[36] studied NB-UVB therapy in 51 children with vitiligo that received twice weekly treatment for a maximum of 1 year, and concluded that NB-UVB therapy was effective and safe in childhood vitiligo and significantly improved the QOL. They recommended that NB-UVB therapy should be applied no longer than 12 months in children.[36] If no response is observed after 6 months, further therapy should be discouraged.[36] If, in responding cases, parents or patients insist on continuing treatment after 1 year, only limited areas should be exposed to NB-UVB radiation.[36] They advocated preventing unnecessary exposure to natural sunlight and using UV-blocking agents on sun-exposed areas.[36] In Japan, no evidence has been obtained regarding the efficacy and safety of NB-UVB therapy for childhood vitiligo. It is recommended that clinicians inform the parents and child patients of the probable effectiveness of NB-UVB therapy and the possible adverse reactions including carcinogenesis.

Currently, carcinogenetic adverse effects due to NB-UVB therapy have not well been elucidated in humans, as carcinogenesis occurs several decades after intense UV radiation. Experimental carcinogenesis has been examined in mice,[40] although the incidence of skin carcinomas varied with different NB-UVB radiation methods and strains of mice. Repeated radiation with the minimal erythema dose of NB-UVB induces more carcinogenesis than that of BB-UVB in mice.[40] NB-UVB therapy can induce repigmentation in vitiligo lesions with fewer radiation sessions than BB-UVB therapy.[41] Evidence is lacking to define the upper limit of radiation sessions for the treatment with NB-UVB for individuals with vitiligo, although the recommended limit of NB-UVB therapy is 12 months or 200 treatments.[36,39] UV exposure occurs during daily life. Therefore, history of sun exposure and sun-induced skin aging should be examined before starting phototherapy with NB-UVB. Dermatologists should decide on the therapeutic strategy of NB-UVB with consideration given to the likelihood of efficacy and adverse reactions. The current standard method for NB-UVB therapy is shown in Figure 5. A subsequent guideline should declare the limit of the total sum and number of sessions of NB-UVB treatment.

The grade of recommendation for the treatment of vitiligo with NB-UVB is B. Convincing results of NB-UVB treatment of vitiligo with evidence level III have been shown.

Phototherapy with 308-nm excimer laser/light. Clinical question 6: Is 308-nm excimer laser/light therapy effective for vitiligo? Recommendation: 308-nm excimer laser/light therapy can be applied to vitiligo lesions in which repigmentation are expected. The treatment features should fully be addressed. Grade of recommendation: C1.

To avoid radiation to the normal areas of skin, 308-nm excimer laser/light therapy can radiate 308-nm UV-B to targeted areas of vitiligo lesions. However, phototherapy requires a large amount of time to radiate huge vitiligo lesions. Therefore, 308-nm excimer laser/light therapy is useful for spotted and patched vitiligo lesions.

The efficacy of 308-nm excimer laser therapy in vitiligo is commonly reported as excellent (>75% repigmentation) in 15–50% of treated lesions.[42] A statistically significant improved response was observed in the UV-sensitive areas (face, neck, back, breast and arm) compared with UV-resistant areas (knees, elbows, wrists, hands, ankles and feet), when sessions were performed twice or thrice weekly for 4–36 weeks.[42] The ultimate rate of repigmentation appears to depend on the total number of sessions and not on their frequency.[43]

Adverse reactions to 308-nm excimer laser/light therapy include mild to severe erythema and occasional blisters. Long-

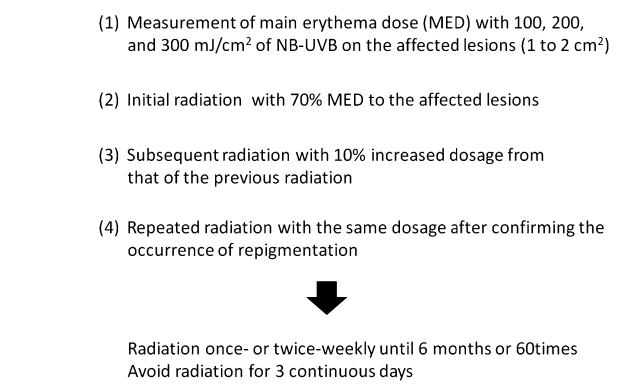

Figure 5. Example of narrowband ultraviolet B therapy.

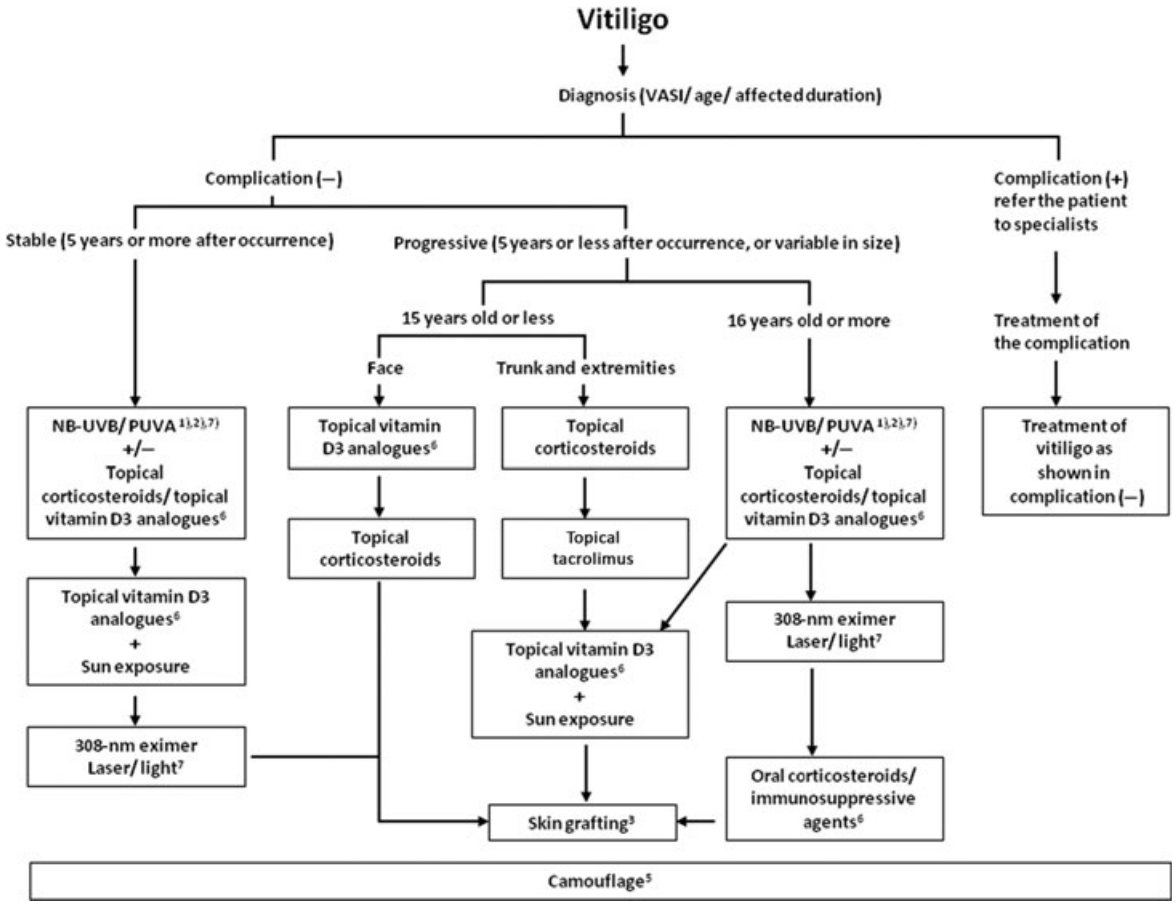

Figure 6. Proposed algorithm for the treatment of vitiligo in Japan. [1]Phototherapy depends on the equipment of each clinic or hospital. [2]Phototherapy should be initiated after considering the affected body surface area, the affected region and the required frequency of visit to each clinic or hospital. [3]Type of skin grafting could be chosen based on the opinion of affected patients after sufficient informed consent is obtained. [4]Combination of topical tacrolimus and phototherapy is currently forbidden in Japan. [5]Camouflage can be applied whenever affected patients wish to use the specific cosmetics. [6]Treatment is not covered by Japanese public health insurance. [7]Treatment should be used for patients aged 16 years or above. NB-UVB, narrowband ultraviolet B; PUVA, psoralen plus ultraviolet A therapy; VASI, Vitiligo Area Scoring Index. [Correction added on 28 March 2013, after first online publication: 'Topical corticosteroids', originally in the second box under 'Trunk and extremities', was changed to 'Topical tacrolimus'.]

standing adverse reactions are difficult to recognize. Long-term follow up of patients receiving 308-nm excimer laser/light therapy would be necessary to examine late-phase adverse reactions.

A randomized, investigator-blinded, half-side comparison study between 308-nm excimer light and NB-UVB phototherapy demonstrated an excellent response rate (>75% repigmentation) in 37.5% of vitiligo patients treated with 308-nm excimer light and in 6% of those treated with NB-UVB.[44]

It is difficult to integrate the findings from studies of 308-nm excimer laser/light therapy applied to vitiligo lesions because the protocols and instruments were different in each study. Furthermore, each study was not designed as a distinct randomized, controlled trial, and had less than 100 participants. In Japan, a controlled, prospective, randomized, double-blinded trial has not been conducted with a sufficient number of vitiligo patients. The efficacy and rate of adverse reactions remain uncertain for 308-nm excimer laser/light therapy in the Japanese population.

The grade of recommendation for the treatment of vitiligo with 308-nm excimer laser/light therapy is C1. This phototherapy can be applied for vitiligo lesions in which repigmentation are expected. Dermatologists using 308-nm excimer laser/light therapy should have enough knowledge of the treatment.

Oral corticosteroids. Clinical question 7: Are oral corticosteroids effective for vitiligo? Recommendation: Oral corticosteroids can be administrated for progressing vitiligo. Grade of recommendation: C1.

Corticosteroids may be administrated p.o. to patients with progressing vitiligo. Few reports with high levels of evidence have been shown. Kim *et al.*[45] studied the efficacy of low-dose oral corticosteroids for vitiligo with a protocol of p.o. prednisolone administration. The dose of oral prednisolone (0.3 mg/kg

bodyweight) was given initially for 2 months, then half of the initial dose was given for the third month, and the dose was halved again for the fourth and final month. This therapy induced repigmentation in 70.4% of vitiligo patients.[45] Seiter *et al.*[46] evaluated the effectiveness of i.v. methylprednisolone (8 mg/kg bodyweight) administrated on 3 consecutive days in vitiligo patients. This therapy induced cessation of disease progression and repigmentation in 71% of vitiligo patients, although re-depigmentation occurred in 10–60% of the affected lesions.

The grade of recommendation for the treatment of vitiligo with oral corticosteroids is C1.

Immunosuppressive agents. Clinical question 8: Are immunosuppressive agents effective for vitiligo? Recommendation: It is impossible to determine the grade of recommendation of immunosuppressive agents for the treatment of vitiligo because only a description was present.[2] Grade of recommendation: Uncertain.

Grafting and surgical treatments. Clinical question 9: Are grafting and surgical treatments effective for vitiligo? Recommendation: Grafting and surgical treatments should only be performed for stable and treatment-resistant vitiligo on cosmetically sensitive regions. Stability refers to no change of the affected lesions for at least more than 1 year. Grade of recommendation: A–C1.

Skin grafts were first used for the treatment of vitiligo in the 1960s and became prevalent in 1980s. This technique has improved through scientific innovation. Currently, five surgical methods are predominant, including: (i) split-thickness skin grafting; (ii) epidermal grafting; (iii) mini-grafting; (iv) autologous non-cultured melanocyte-keratinocyte cell transplantation/injection; and (v) autologous cultured melanocyte transplantation/injection. In 1998, Njoo *et al.*[47] summarized the efficacy of skin grafts in 1035 vitiligo patients in 39 published papers: (i) split-thickness skin grafts were 87% effective (201/232 cases); (ii) epidermal grafts were 87% effective (301/347 cases); and (iii) mini-grafts were 68% effective (175/258 cases).

In 2008, the guideline for the diagnosis and management of vitiligo in the UK proposed the following recommendations:[39] (i) surgical treatment should be used only for cosmetically sensitive sites where there have been no new lesions, no Koebner's phenomenon and no extension of the lesion in the previous 12 months;[39] (ii) s-skin grafting is the best option when a surgical treatment is required;[39] (iii) mini-graft is not recommended due to a high incidence of side-effects and poor cosmetic results, including cobblestone and polka-dot appearance;[39] and (iv) autologous epidermal suspension applied to laser-abraded lesions followed by NB-UVB or PUVA therapy is the optimal surgical transplantation procedure, but it does require special facilities.[39]

The first recommendation is acceptable. If Koebner's phenomenon occurs, donor sites may result in vitiligo. However, the second to fourth recommendations should be discussed. The second recommendation introduced the effectiveness of split-skin grafting. However, ultrathin split-thickness skin grafting or epidermal grafting is usually applied for the treatment of vitiligo. If typical split-thickness skin grafting is used, donor sites may result in scarring as observed in the treatment of skin ulcer or burn. Actually, split-thickness skin grafting is rarely applied for vitiligo.[48] The third recommendation denied the effectiveness of mini-grafting. Nevertheless, mini-grafting is the simplest and most commonly used surgical method for vitiligo repigmentation.[48] Cobblestone appearance rarely occurs if the procedure is performed appropriately.[48] For facial lesions, 1.0-mm mini-grafts are recommended, and 1.2-mm mini-grafts are recommended for other areas.[48] The procedure of the elimination of the subcutis of mini-grafts further diminishes the possibility of cobblestone appearance.

The treatment of vitiligo has improved with the use of epithelial cell suspensions (ReCell, Spray-On Skin; Avita Medical, Cambridge, UK) for autologous non-cultured melanocyte-keratinocyte cell transplantation/injection and autologous cultured melanocyte transplantation/injection. Improvement of suction blister roof grafting was also reported.[49] It is expected that further improvement would result in better prognosis for the treatment of vitiligo, particularly in the cosmetically sensitive regions.

The grade of recommendation for the treatment of vitiligo with grafting and surgical treatments is A–C1. Grafting should only be performed for stable and treatment-resistant vitiligo present on cosmetically sensitive regions. The current prevalent techniques include ultrathin split-thickness skin grafting, epidermal grafting and 1-mm mini-grafting. In the near future, more advanced and novel techniques will be introduced.

Camouflage. Clinical question 10: Is camouflage effective for vitiligo? Recommendation: Camouflage is valuable in improving QOL. Camouflage cannot cure vitiligo. Japanese public health insurance does not cover camouflage. Grade of recommendation: C1.

Vitiligo lesions on cosmetically sensitive regions tend to result in QOL impairment in affected patients. Ongenae *et al.*[50] showed that camouflage may be recommended, particularly in vitiligo patients with higher Dermatology Life Quality Index scores or self-assessed disease severity, as patients with minor involvement of the face benefit from camouflage. Tanioka *et al.*[51] supported the idea that camouflage for patients with vitiligo not only covers the white patches but also improves their QOL. Camouflage cannot cure vitiligo. Japanese public health insurance does not cover camouflage.

The grade of recommendation for the treatment of vitiligo with camouflage is C1. Camouflage can be used for vitiligo lesions in which QOL would be improved. Specific cosmetics are recommended as camouflage for vitiligo.

Topical bleaching agents. Clinical question 11: Are topical bleaching agents useful for generalized stable vitiligo? Recommendation: Topical bleaching agents may be applicable for generalized stable and treatment-resistant vitiligo to improve QOL. Grade of recommendation: C1.

Patients with generalized vitiligo are advised to receive medications to induce repigmentation or camouflaging. Topical bleaching agents occasionally may be applied to unaffected skin in patients who do not recover their skin color with various treatments and experience QOL impairment due to camouflage. Hydroquinone monobenzyl ether (*p*-[benzyloxy] phenol) is applied to normal skin to bleach the color of normal skin to match the depigmented color of vitiligo. The evidence level for this recommendation is low because no scientific statistic data have been reported. Hydroquinone monobenzyl ether may induce irritation and contact dermatitis.

Japanese public health insurance does not cover this treatment. Import of hydroquinone monobenzyl ether ointment/cream is needed or is produced by the dermatologists themselves. Topical bleaching agents may be applicable for generalized stable and treatment-resistant vitiligo in order to improve QOL. Informed consent should be obtained cautiously, with explanation of the possibility of irritated sensitization during application, persistent depigmentation on the treated normal skin, recovery of repigmentation on the affected lesions and lack of coverage by Japanese public health insurance.

The grade of recommendation for the treatment of vitiligo with topical bleaching agents is C1.

Algorithm for the treatment of vitiligo and depigmented disorders

This algorithm for the treatment of vitiligo was proposed after discussing the levels of evidence, severity of vitiligo and leukoderma, strategy of treatment, prevention of adverse reactions, and the period of the treatment with reference to published papers (Fig. 6). The current treatment of congenital depigmented disorders is only effective with surgical treatment and camouflage. Therefore, the algorithm focused on vitiligo. Phototherapy was proposed with respect to the skin color of the Japanese population, adaptive criteria and prevention of adverse reactions with reference to the guideline for the diagnosis and treatment of psoriasis in Japan.

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