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Review Article

Treatment of vitiligo: medical treatment, phototherapy and surgical treatment

白蝕的治療：藥物治療、光療及手術治療

ECY Chu 朱灼欣

Vitiligo is a depigmentary disorder which causes significant psychological distress. Treatment of vitiligo aims to minimise disease progression and achieve cosmetically pleasing repigmentation. Topical corticosteroids are commonly used as the first-line therapy. Studies showed that topical calcineurin inhibitors and topical vitamin D3 analogues are also effective treatment options of vitiligo. Phototherapy should be reserved for patients who fail topical therapy. For the group of patients not responding to conservative treatment modalities, surgical treatment is the only option. Understanding all the available treatment options helps us to choose the appropriate treatment for our patients.

白蝕是一種可引致顯著心理困擾的皮膚色素脱失症。其治療目的是盡力防止患處擴大，同時使脱色部位達致美容上令人滿意的膚色復原。外用皮質類固醇是常用的第一線治療。研究發現外用鈣調神經磷酸酶抑製劑和外用維生素D3類似物亦是有效的外用治療選擇。光療則應留待給對外用藥物治療無效者。如果連光療亦不見效，手術治療便是終極的選擇。只要了解所有可用的療法，我們便能爲白蝕病人選擇最適切的治療方案。

Keywords: Depigmentation, medical treatment, phototherapy, surgical treatment, vitiligo

關鍵詞：色素脱失、藥物治療、光療、手術治療、白蝕

Social Hygiene Service, Department of Health, Hong Kong

ECY Chu, FHKCP, FHKAM

Correspondence to: Dr. ECY Chu

Wan Chai Social Hygiene Clinic, 7/F Tang Chi Ngong Specialist Clinic, 284 Queen's Road East, Wan Chai, Hong Kong

Introduction

Vitiligo is a depigmentary disorder which can be disfiguring, leading to significant psychological distress. It is a multifactorial polygenic disorder. Its precise cause remains unknown. The autoimmune hypothesis is the best supported theory. The treatment of vitiligo aims to minimise

the disease progression, to attain repigmentation and to achieve cosmetically pleasing result. Treatment options include medical treatment, phototherapy and surgical treatment.

Topical corticosteroids

For medical treatment, topical corticosteroids are commonly used as the first-line treatment. Their efficacy is attributed to modulation of the immune response. Based on comparative studies, topical corticosteroids are the most clinically effective choice for topical therapy. Kwinter et al reported response rates of 64% with complete repigmentation rates as high as 49.3%.[1] When used with UVA phototherapy, the repigmentation rate is enhanced. Systemic corticosteroids are not considered as conventional treatment for vitiligo. However, Seiter et al found that administering methylprednisolone 8 mg/kg intravenously for three days in patients with generalised vitiligo led to cessation of disease progression in 85% and repigmentation in 71%.[2] The lack of data on the efficacy and optimal dosing parameters warrants further research. Side effects of topical corticosteroids include epidermal atrophy, telangiectasia, striae, folliculitis, glaucoma, cataract and the side effects associated with systemic absorption. The side effects prohibit long-term use of steroid and merit frequent monitoring and regular steroid holidays.

Topical calcineurin inhibitors

Topical calcineurin inhibitors provide similar to slightly inferior results comparing with topical corticosteroids. Many small clinical studies support the efficacy of topical tacrolimus and pimecrolimus when assessed after three and six months of therapy. The response rates range from 63% to 89% with mean repigmentation rates ranging from 26% to 72.5%. The best results are seen on the head and neck region.[1] There is little data on the use of systemic ciclosporin in the treatment of vitiligo.

Passeron et al showed that that the combination of topical tacrolimus ointment with NBUVB could lead to repigmentation rates of more than 50% in 42% of lesions in patients with chronic stable refractory vitiligo.[3] The authors found that combining topical tacrolimus with 308-nm excimer laser produced a 100% response rate with 70% achieving more than 75% repigmentation while the response rate was 75% in those treated with light only.[3]

Topical vitamin D analogue

Calcipotriene is a topical vitamin D3 analogue with several different mechanisms of action. It acts through its anti-proliferative effect on keratinocytes in treating psoriasis while its immunomodulatory effects and its ability to enhance melanocyte development led to its role as a treatment option for vitiligo. Most studies evaluated calcipotriene as an adjuvant therapy. Small clinical trials of calcipotriene monotherapy in children showed response rates as high as 77% with complete repigmentation in 16% of patients.[4] Compared to topical corticosteroids, calcipotriene has lower response and repigmentation rates. When it is combined with topical corticosteorids, the repigmentation rates increase, the delay in the onset of repigmentation is decreased, and there is a greater stability of repigmentation when compared with either as a monotherapy.[5] The impact of calcipotriene on light phototherapy is controversial. In general, topical calcipotriene is considered as safe, as only infrequent and mild irritation is reported.

Phototherapy

For phototherapy, ultraviolet light has been used to treat patients with vitiligo since the 1800s. The exact mechanism of action is unknown. *In vitro* studies have shown that both UVA and UVB phototherapies promote a favourable environment for the growth of melanocytes and inhibit autoimmunity. UVA phototherapy is almost always

given in conjunction with the photosensitiser psoralens (PUVA). PUVA is approved by the FDA for the treatment of vitiligo. High dose of UVA alone (15 J/cm^2) induces repigmentation in half of the subjects; when enhanced with psoralen, the response rates are as high as 78%.[6] Photochemotherapy with topical psoralen can be used in patients with small lesions or who are younger than 12 years old in whom systemic PUVA phototherapy is contraindicated. Adisen et al found no significant difference in the number of treatments, response rates and mean cumulative dose of topical PUVA compared with oral PUVA in patients with vitiligo.[7] In the past decades, NBUVB phototherapy has superseded PUVA phototherapy in the treatment of vitiligo. Studies have proven that NBUVB phototherapy is superior to PUVA phototherapy in producing disease stability and repigmentation. However, PUVA phototherapy may yield quicker results.[8] The regular maintenance and calibration of phototherapy machines is crucial to ensure proper dose delivery. Dosimetry is more demanding than with other indications because of the increased photosensitivity of vitiliginous skin.

Laser therapy

Laser therapy is a relatively new treatment of vitiligo that has gained popularity in the last decade. The mechanism of action is thought to be similar to conventional light therapy, but lasers allow targeted treatment, less total body irradiation and less impact on the healthy skin. Monochromatic excimer laser (MEL) is the best studied and most used laser therapy for vitiligo. MEL is a nonablative technology that emits light in the UV range. The xenon chloride MEL emits a 308-nm wavelength, very similar to the 311-nm of NBUVB. The MEL is approved by the FDA for treating vitiligo. When MEL is used as a monotherapy, repigmentation rates of more than 75% are seen in 16.6% to 52.8% of patients, the response rates are as high as 95%.[9] In most clinical trials, MEL is used one to three times a week for an initial course of 12 weeks. On average, it takes 11 to 22 sessions to see repigmentation. Combination therapy with topical corticosteroid or topical tacrolimus has been shown to have an additive effect.

Bioskin

Bioskin is a relatively new device from Italy. It is not currently widely available. Bioskin provides focused 311-nm UVB phototherapy (microphototherapy). A large study of 458 subjects compared Bioskin with several other conventional topical therapies. When Bioskin was used alone, Bioskin had repigmentation rates of more than 75% in 72% of patients. In combination, the best result was seen with betamethasone dipropionate with >75% repigmentation in 90.2% of subjects. All other tested modalities had improved repigmentation rates when used in combination with Bioskin comparing with its use as a monotherapy.[10]

Antioxidants

Oxidative stress has been implicated in the pathogenesis of vitiligo and methionine sulphoxide (MSR), an important reducing agent in repairing damage caused by reactive oxidative species, is found less active and present in lower amount in patients with vitiligo. Topical and oral antioxidants may have a role in protecting melanocytes from destruction by reactive oxygen species. Studies suggest that antioxidants are an effective, inexpensive and well-tolerated form of treatment for vitiligo. In a double-blind, placebo-controlled trial, monotherapy with oral ginkgo significantly decreased disease progression compared with placebo and was shown to produce moderate to complete repigmentation in 40% (10 out of 25) of patients.[11] Dell'Anna et al revealed that supplementing NBUVB phototherapy with a combination of alpha-lipoic acid, vitamin C, vitamin E and polyunsaturated fatty acids improved response rates (>75% repigmentation) from 18% to 47%.[12] Catalase also has antioxidant

properties, while one case study showed a remarkable repigmentation response on the face and hands of patients using a combination of topical pseudocatalase and short-term UVB phototherapy (complete repigmentation in 90%, all active depigmentation was arrested), however, other studies showed no such benefit.[13]

Surgical treatments

For the group of patients not responding to conservative treatment, surgical treatment is another treatment option. Surgical treatments can be in the form of tissue grafting by means of blister graft, split-thickness skin graft or punch graft or in the form of cellular grafting. For blister grafting, blisters can be produced by various methods. Suction blisters created by the use of small vacuum pumps are widely used as these can be easily used in the outpatient setting. The blister is deroofed, cut to the appropriate size and shape and then transplanted onto the recipient site. The recipient site must be prepared to enable proper adherence and uptake of the graft. Repigmentation spreads outward from the graft. The cosmetic response to suction blister grafting is very good. Hatchome et al found that pigmentation from the graft had a two- to threefold expansion to the surrounding tissue after three to four months in most patients.[14] The split-thickness skin graft (STSG) is less popular than the blister graft, but it has a major advantage of being able to cover large areas with a single surgical procedure. The graft is harvested with the assistance of a dermatome which creates a graft of uniform thickness. It is then meshed to prevent seroma formation and to cover a greater area. It is placed over a dermabraded recipient site and dressed in gauze. Agrawal et al treated 32 sites in 21 patients with stable refractory vitiligo using STSG, of which 69% of lesions responded with 100% repigmentation while the remainder achieved 90-95% repigmentation.[15] STSG however requires the use of anaesthesia and can result in cosmetically undesirable harvest sites. Punch grafting or mini punch grafting is one of the most commonly used techniques. Multiple tiny punch grafts are harvested and placed onto the recipient site that was either dermabraded or perforated with a similar size punch. In one large study which recruited 1000 patients, there was 90-100% repigmentation in 74.5% of the patients.[16] Cellular grafting can be performed in the form of cultured or non-cultured cellular grafting. The essence of the autologous melanocyte suspension transplant (AMST) is to harvest tissue from a donor site, release individual cells into a suspension and then transplant onto the de-epithelialised recipient skin. Either melanocytes only or both keratinocytes and melanocytes can be transplanted. Cellular culturing has been used to increase the number of viable cells for transplant while less donor tissue is needed. In a study of non-cultured melanocyte-keratinocyte cell transplantation, Mulekar found that 56% of patients achieved repigmentation rates of more than 95% and the repigmentation was maintained at six years of follow up.[17] AMST is an alternative to tissue grafting but preparation of the suspension is complicated and time-consuming.

Depigmentation

Depigmentation can be considered in patients who fail repigmentation therapy or have extensive disease. Topical agents including monobenzone and hydroquinone are approved by the FDA for this purpose. They may cause a burning sensation, itch and contact dermatitis. The Q-switched ruby laser and the Q-switched alexandrite laser can be used alone or in combination with topical depigmentating agents. The depigmentating effect may not be permanent. Further studies are required to determine the optimal frequency and duration of laser therapy.

Camouflage

Camouflage can help to create a cosmetically pleasing appearance. It should be recommended to patients at all stages of treatment and can be

temporary in the form of makeup, semi-permanent in the form of self-tanning agents and permanent in the form of a tattoo.

Conclusion

With different treatment modalities, treatment should start with the less aggressive and cost effective modalities, while reserving the more invasive and expensive options for those who fail first-line therapies. First-line treatment includes topical corticosteroid, topical calcineurin inhibitors and topical vitamin D3 analogues. NBUVB is an effective treatment for vitiligo and used as a second-line therapy. For those not responding to conservative treatment, surgical treatment can be considered. Surgical treatment can be in the form of tissue grafting or cellular grafting. Camouflage should be recommended to patients at all stages of treatment. Depigmentation can be considered in patients with extensive disease or who cannot attain cosmetically acceptable outcome with all stages of treatment.

References

1. Kwinter J, Pelletier J, Khambalia A, Pope E. High-potency steroid use in children with vitiligo: a retrospective study. J Am Acad Dermatol 2007;56:236-41.
2. Seiter S, Ugurel S, Tilgen U, Reinhold U. Use of high-dose methylprednisolone pulse therapy in patients with progressive and stable vitiligo. Int J Dermatol 2000; 39:624-7.
3. Passeron T, Ostovavi N, Zakaria W, Fontas E, Larrouy JC, Lacour JP, et al. Topical tacrolimus and the 308-nm excimer laser: a synergistic combination for the treatment of vitiligo. Arch Dermatol 2004;140: 1065-9.
4. Parsad, Saini R, Nagpal R. Calcipotriol in vitiligo: a preliminary study. Pediatr Dermatol 1999;16:317-20.
5. Kumaran MS, Kaur I, Kumar B. Effect of topical calcipotriol, betamethasone dipropionate and their combination in the treatment of localized vitiligo. J Eur Acad Dermatol Venereol 2006;20:269-73.
6. El-Mofty M, Mostafa W, Youssef R, El-Fangary M, Elramly AZ, Malgoub D. Ultraviolet A in vitiligo. Photodermatol Photoimmunol Photomed 2006;22:214-6.
7. Adisen E, Karaca F, Oztas M, Gurer MA. Efficacy of local psoralen ultraviolet A treatments in psoriasis, vitiligo and eczema. Clin Exp Dermatol 2008;33: 344-5.
8. Bhatnagar A, Kanwar AJ, Parsada D, De D. Psoralen and ultraviolet A and narrow-band ultraviolet B inducing stability in vitiligo, assessed by vitiligo disease activity score: an open prospective comparative study. J Eur Acad Dermatol Venereol 2007;21:1381-5.
9. Hadi SM, Spencer JM, Lebwohl M. The use of the 308-nm excimer laser for the treatment of vitiligo. Dermatol Surg 2004;30:983-6.
10. Lotti T, Buggiani G, Troiano M, Assad GB, Delescluse J, De Giorgi V, et al, Targeted and combination treatments for vitiligo. Comparative evaluation of different current modalities in 458 subjects. Dermatol Ther 2008;21: S20-6.
11. Parsad D, Pandho R, Juneja A. Effectiveness of oral ginkgo biloba in treating limited, slowly spreading vitiligo. Clin Exp Dermatol 2003;28:285-7.
12. Dell'Anna ML, Mastrofrancesco A, Sala R, Venturini M, Ottarian M, Vidolin AP, et al. Antioxidants and narrow band-UVB in the treatment of vitiligo: a double-blind placebo controlled trial. Clin Exp Dermatol 2007;32: 631-6.
13. Schallreuter KU, Wood JM, Lemlce KR, Levering C. Treatment of vitiligo with a topical applicaton od pseudocatalase and calcium in combination with short-term UVB exposure: a case study of 33 patients. Dermatology 1995;190:223-9.
14. Hatchome N, Kato T, Tagami H. Therapeutic success of epidermal grafting in generalized vitiligo is limited by the Koebner phenomenon. J Am Acad Dermatol 1990; 22:87-91.
15. Agrawal K, Agrawal A. Vitiligo: repigmentation with dermabrasion and thin split-thickness skin graft. Dermatol Surg 1995;21:295-300.
16. Malakar S, Dhars S. Treatment of stable and recalcitrant vitiligo by autologous miniature punch grafting: a prospective study of 1000 patients. Dermatology 1999; 198:133-9.
17. Mulekar SV. Long-term follow-up study of 142 patients with vitiligo vulgaris treated by autologous, non-cultured melanocyte-keratinocyte cell transplantation. Int J Dermatol 2005;44:841-5.