CHAPTER 54
Vitiligo

Juan Jorge Manriquez and Sergio M. Niklitschek
Department of Dermatology, Pontificia Universidad Catolica de Chile, Santiago, Chile

UNCORRECTED PROOFS

Background

Definition
Vitiligo is an acquired disorder of pigmentation mainly affecting the skin, in which the loss of functioning melanocytes results in white patches.

Incidence/prevalence
Vitiligo is a common skin disorder, affecting about 0.5% of the general population, irrespective of ethnic origin [1].

Etiology
There appears to be a genetic predisposition to vitiligo, consistent with a polygenic disorder. However, the pathogenesis of vitiligo still remains unknown. The main hypothesis theorizes an autoimmune process against melanocytes. Other theories include an intrinsic abnormality of melanocytes [2], toxic effect of free radicals [3], an increased release of catecholamines locally [4], and cytomegalovirus infection [5].

Prognosis
Although neither lethal nor symptomatic, the effects of vitiligo can be cosmetically and psychologically devastating. The course of the disease is fairly unpredictable, but often progressive [6].

Diagnosis
The diagnosis is clinical and based upon the presence of skin patches devoid of pigment.

Aim of treatment
The aim of treatment is to achieve partial or total repigmentation, at least for body areas that the patients estimate as "most significant," with minimal adverse effects.

Relevant outcomes
- Physician-rated clinical response: success rate in terms of repigmentation (>75%) and long-term repigmentation rate.
- Side effects of treatment.

Methods of search
We searched for randomized controlled trials (RCTs) of currently available medical and surgical treatments at the Cochrane Central Register of Controlled Trials, Medline, and Embase, using the keyword "vitiligo." The search was completed in June 2012. Where no RCTs were found, information from nonrandomized studies or case series was used.

A Cochrane systematic review (search date November 2009) and a *British Medical Journal* Clinical Evidence systematic review (search date March 2010) were used as a source of RCTs [7,8].

Questions

What are the effects of medical treatment in vitiligo?

Case scenario

A 26-year-old woman reports a 10-year history of depigmented areas. Clinical examination reveals symmetrically distributed depigmented areas affecting the sun-exposed areas, mainly upper arms, face and neck (Figure 54.1).

Topical therapies

Topical corticosteroids One RCT [9] compared topical clobetasol propionate with psoralen plus sunlight therapy (PUVAsol). Participants receiving clobetasol propionate were significantly more likely than those receiving PUVAsol to achieve greater than 75% repigmentation (risk ratio [RR], 4.70; 95% confidence interval [CI],

Evidence-Based Dermatology, Third Edition. Edited by Hywel C. Williams, Michael Bigby, Andrew Herxheimer, Luigi Naldi, Berthold Rzany, Robert Dellavalle, Yuping Ran, and Masutaka Furue.
© 2014 John Wiley & Sons, Ltd. Published 2014 by John Wiley & Sons, Ltd.

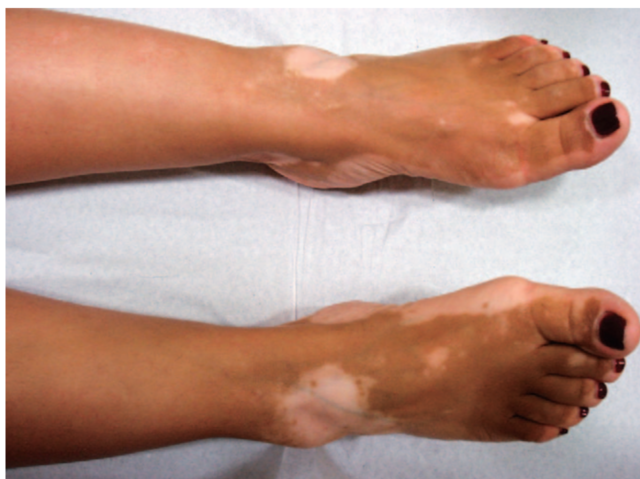

Figure 54.1 Achromic areas on feet of a 35-year-old woman with vitiligo.

1.14–19.39). Another study [10] compared topical clobetasol propionate plus narrowband UVB phototherapy (NB-UVB) versus placebo plus NB-UVB. There was no statistically significant difference between the two groups. One RCT [11] compared topical hydrocortisone plus 308 nm monochromatic excimer light (MEL) versus MEL alone. Participants receiving the combination treatment were more prone to achieve 75% repigmentation than those receiving laser treatment alone (RR, 2.57; 95% CI, 1.20–5.50).

One RCT [12] compared topical betamethasone dipropionate with either calcipotriol or betamethasone dipropionate plus calcipotriol. None of the participants achieved greater than 75% repigmentation.

One RCT [13] found topical clobetasol to be more effective than topical pimecrolimus in the mean percentage of repigmentation (57.7% vs 32.1%, respectively; $P < 0.05$) after 8 weeks of treatment.

One RCT [14] showed no statistically significant difference between topical clobetasol propionate and 0.1% tacrolimus with respect to repigmentation greater than 75%. One RCT [15] compared topical fluticasone propionate (FP) versus FP plus UVA phototherapy or versus UVA alone. No significant difference was seen between participants in the FP plus UVA group and those receiving FP alone in achieving greater than 75% repigmentation. FP alone and with UVA was superior to UVA alone (RR, 3.94; 95% CI, 1.16–13.43).

Topical class 3 corticosteroids have been shown to be effective in localized vitiligo, with a pooled odds ratio (OR) [16] of 14.3 (three RCTs [17–19]; 95% CI, 2.4–83.7); pooled ORs showed nonsignificant differences between topical class 4 or intralesional corticosteroids and their respective placebos [16].

One RCT [20] found that a combination of topical clobetasol and estrogen could be more effective than clobetasol alone in reducing the average area of lesions after 3 months' treatment ($P < 0.001$).

Drawbacks All studies examining the effect of topical corticosteroids reported adverse effects, with the more frequent being atrophy, telangiectasia, hypertrichosis, and acneiform papules.

Intralesional corticosteroids One study [21] assessed the rate of adverse effects of triamcinolone acetonide injections versus placebo injections and found atrophy in eight participants, telangiectasia in two, infection in one, and intradermal hemorrhage in one.

Topical vitamin D analogues: calcipotriol and tacalcitol Only one RCT [12] examined the effect of calcipotriol as monotherapy (see Topical corticosteroids section).

One RCT [22] compared calcipotriol plus PUVAsol with placebo plus PUVAsol. There was no statistically significant difference in the number of participants achieving greater than 75% repigmentation. One RCT [23] compared calcipotriol plus psoralen plus UVA phototherapy (PUVA) with placebo plus PUVA. The side of participants treated with the calcipotriol plus PUVA had a significant fourfold increase in the likelihood of achieving greater than 75% repigmentation sooner than the side treated with placebo plus PUVA (paired OR 4.25; 95% CI, 1.43–12.64). One RCT [24] compared tacalcitol plus MEL with placebo plus MEL. A statistically significantly greater proportion of participants in the tacalcitol plus MEL group achieved greater than 75% repigmentation (RR, 4.50; 95% CI, 1.05–19.35). Another RCT [25] compared tacalcitol plus sunlight versus placebo plus sunlight, but found no difference between the groups.

One study [26] found no significant differences between calcipotriol combined with NB-UVB and NB-UVB alone in achieving repigmentation of lesions.

One RCT [27] compared the effectiveness of NB-UVB alone and combined with tacalcitol. Addition of topical tacalcitol to NB-UVB improved the extent of repigmentation and increased the response rate.

Drawbacks The more frequent adverse effects in associated with topical vitamin D analogues were mild skin irritation, xerosis (dryness), and itching.

Calcineurin inhibitors: tacrolimus and pimecrolimus Only one RCT [14] examined the effect of topical tacrolimus as monotherapy (see Topical corticosteroids section).

A meta-analysis [28] from two studies [28,29] found that topical 0.1% tacrolimus plus MEL was more effective than placebo plus MEL in achieving 75% repigmentation (RR, 3.15; 95% CI, 1.46–6.76).

One RCT [30] compared topical pimecrolimus plus NB-UVB versus placebo plus NB-UVB, finding no statistically significant difference in rates of repigmentation (RR, 3.38; 95% CI, 0.93–12.29).

One RCT [31] found pimecrolimus 1% cream and microdermabrasion to be more effective than pimecrolimus 1% cream alone in achieving more than 50% of pigmentation of the treated patches (60.4% vs 32.1%; $P < 0.001$), over 3 months of follow-up.

Drawbacks The more frequent adverse effects in associated with topical calcineurin inhibitor were burning sensations, erythema, and localized bullous eruptions.

The United States Food and Drug Administration has warned of a potential malignancy risk from the use of topical tacrolimus and pimecrolimus, principally based on the theoretical risk of immunomodulator utilization. A systematic review and a case–control study were not able to confirm such an association in individuals being treated for atopic eczema [32,33].

Khellin One RCT [34] compared the application of khellin in two different vehicles plus UVA versus the vehicles alone plus UVA.

UNCORRECTED PROOFS

There was no statistically significant difference in repigmentation between any intervention. No significant differences were found in a trial [35] that compared oral khellin and placebo plus sunlight.

Pseudocatalase and catalase/dismutase superoxide One study [36] compared Dead Sea climatotherapy plus pseudocatalase cream with Dead Sea climatotherapy plus placebo cream and Dead Sea climatotherapy alone. However, this study did not examine any outcomes of interest. One RCT [37] reported a self-limiting erythematous papular rash in one participant treated with a topical catalase/dismutase superoxide, but did not examine any other outcomes of interest.

Melagenina (human placental extract) One study [38] examined the effects of melagenina. However, the study examined no outcomes of interest.

Comments/implications for practice It appears reasonable to regard topical corticosteroids as the first-line treatment for localized vitiligo. Topical vitamin D analogues may be an alternative given in combination with light therapies.

Topical tacrolimus seems to be a useful tool, especially for the management of facial skin or eyelid lesions, where the risk of skin atrophy from topical corticosteroids or phototoxicity from phototherapy could be high.

No clear recommendations on the use of khellin, pseudocatalase and catalase/dismutase superoxide, and melagenina can be made on the basis of the current evidence.

Oral therapies

One RCT [39] examined the effect oral *Ginkgo biloba*, compared with placebo. Overall, *Ginkgo biloba* showed a significant improvement over placebo (RR, 4.40; 95% CI, 1.08–17.95).

One RCT [40] compared the effect of oral minipulses of betamethasone (OMB) with three different combinations of interventions: OMB plus PUVA; OMB plus NB-UVB, and OMB plus broadband UVB phototherapy. There was a statistically significant difference in favor of OMB plus NB-UVB compared with OMP alone (RR, 7.41; 95% CI, 1.03–53.26), but not for OMB plus PUVA versus OMB alone or for OMB plus broadband UVB phototherapy versus OMB alone.

One RCT [41] compared oral azathioprine plus PUVA versus PUVA alone. The combination scheme was statistically significantly more likely to achieve greater than 75% repigmentation (RR, 17.77; 95% CI, 1.08–291.82).

One RCT [42] compared an oral antioxidant pool plus NB-UVB with NB-UVB alone. No statistically significant difference was found between the two groups.

Two RCTs [43,44] found no differences in a quality-of-life index between the use of *Polypodium leucotomos* plus NB-UVB and placebo plus NB-UVB, or between the use of oral levamisole plus topical mometasone furoate and oral placebo plus topical mometasone.

One RCT [45] compared the effectiveness of oral L-phenylalanine, with and without UVA. There was no statistically significant difference between the L-phenylalanine plus UVA group and the no active treatment group, or between the L-phenylalanine alone group versus the no active treatment group.

One RCT [46] compared oral vitamin B12 and folic acid plus NB-UVB with NB-UVB alone. The addition of vitamin B12 and folic acid did not improve any outcome.

Drawbacks Nausea was reported with L-phenylalanine, NB-UVB plus *Polypodium leucotomos*, and *Ginkgo biloba*. Weight gain was reported in subjects treated with minipulses of betamethasone.

Comments/implications for practice Systemic corticosteroids are not recommended, not only because of the limited evidence of their effectiveness, but also because of the wide range of adverse effects associated with them.

More long-term studies are needed in order to establish the effectiveness and safety profile of oral *Ginkgo biloba* and the possible additive effect of azathioprine when used with light therapies.

No clear recommendations on the use of oral antioxidants or levamisole can be made on the basis of the current evidence.

Light therapies

Oral psoralen plus ultraviolet A There was no statistical difference in repigmentation in participants treated with PUVA compared with NB-UVB [47].

One RCT assessed PUVA in combination with calcipotriol [23] (see Topical vitamin D analogues section). One RCT assessed oral PUVA in combination with azathioprine [41] (see Topical vitamin D analogues section).

Drawbacks The more frequent adverse effects associated with PUVA were sedation, xerosis, erythema, exacerbation of acne lesions, and nausea.

Psoralen plus sunlight therapy One RCT [48] compared different psoralen compounds, doses, and combinations, combined with exposure to sunlight. One RCT [49] compared oral trimethylpsoralen (TMP) plus sunlight/sun lamp with placebo and the same light exposure in children. One study [50] compared oral PUVAsol versus topical PUVAsol versus oral triamcinolone combined with PUVAsol. One RCT [22] compared topical calcipotriol plus PUVAsol with placebo combined with PUVAsol (see Topical vitamin D analogues section). One RCT [40] evaluated OMB plus PUVA, OMB plus NB-UVB, OMB plus BB-UVB, or OMB alone (see Oral therapies section); and one RCT [51] assessed minipunch grafting plus PUVAsol versus split-skin grafting plus PUVAsol.

Only two of the numerous comparisons of different psoralen compounds combined with exposure to sunlight were statistically significant and were based on data from one trial [48]: methoxypsoralen plus TMP versus psoralen plus sunlight (RR, 0.35; 95% CI, 0.14–0.87) and methoxypsoralen plus sunlight versus psoralen (RR, 2.50; 95% CI, 1.06–5.91).

Drawbacks Adverse effects reported were nausea, pruritus, dizziness, headaches, eye discomfort, and vague gastrointestinal symptoms. There was no evidence of liver or blood toxicity in either group.

Ultraviolet A See Topical corticosteroids section.

Drawbacks One RCT [15] reported a mild atrophy in areas treated with UVA.

Ultraviolet B In one RCT [52] none of the 10 participants receiving either NB-UVB or BB-UVB showed greater than 75% repigmentation after 12 weeks of treatment.

UNCORRECTED PROOFS

In another RCT, there were no statistical differences in repigmentation in participants treated with MEL from those treated with NB-UVB [53].

In one study, the combined therapy (5-fluorouracil plus Er-YAG laser plus NB-UVB) showed more repigmentation than NB-UVB phototherapy alone (RR, 5.60; 95% CI, 2.31–13.59) [54].

The outcomes for other studies are listed in the Oral therapies section [40,42,46], the Topical corticosteroids section [10], and the Calcineurin inhibitors section [30].

One RCT [55] found no significant differences in repigmentation between NB-UVB light plus a topical formulation including *Cucumis melo* superoxide dismutase and catalase (Vitix), and NB-UVB light alone.

One RCT [56] found no significant differences in repigmentation between pseudocatalase cream and NB-UVB versus placebo and NB-UVB.

One RCT [57] found no significant differences in repigmentation between NB-UVB, topical pimecrolimus, and tacrolimus.

One RCT [58] found no differences in degrees of repigmentation between targeted NB-UVB plus topical tetrahydrocurcuminoid versus targeted NB-UVB alone.

One RCT [59] compared the efficacy of topical PUVA versus NB-UVB. The treatment with NB-UVB was as efficient as with topical PUVA and had fewer adverse effects.

Drawbacks Adverse effects associated with UVB phototherapy were itching, hyperpigmentation and mild phototoxic effects.

Lasers One RCT [60] evaluated three different regimens of MEL. Repigmentation initiation correlated with treatment number, regardless of frequency. However, repigmentation occurred earlier in the most frequently treated lesions ($P = 0.0336$).

Laser therapies associated with tacrolimus [28,29] (see Calcineurin inhibitors section), topical calcipotriol [61] (see Topical vitamin D analogues section), and topical hydrocortisone [11] (see Topical corticosteroids section) were evaluated.

Three RCTs evaluated percentage of repigmentation >75% [28,29] (see Calcineurin inhibitors section) [11]; (see Topical corticosteroids section).

One RCT [62] found that a combination of MEL and topical 1% pimecrolimus was more effective than only MEL in achieving repigmentation.

Drawbacks Laser therapy was associated with burning and/or stinging, moderate to severe erythema, blisters, and edema.

Comments/implications for clinical practice On the basis of the current evidence it appears reasonable to regard NB-UVB – alone or plus tacalcitol – as the first-line treatment for moderate to severe generalized vitiligo.

Treatment with MEL, alone or in combination with topical vitamin D analogues, tacrolimus, or topical corticosteroids, seems reasonable according to current evidence, but its utilization may be reduced because of its availability.

Surgical interventions

Suction blister grafts One RCT [63] compared suction blister grafts with thin split-thickness grafts. Although repigmentation rates were compared, the study did not assess the primary outcome greater than 75% repigmentation. The only outcome of interest was adverse effects.

In another RCT [64], participants either underwent transplantation of cultured autologous melanocytes plus PUVA therapy (CMP) on one limb and PUVA only (PO) on another, or suction blister transplantation plus PUVA (SBP) on one limb and cryotherapy plus PUVA (CP) on another (see Oral psoralen plus ultraviolet A section).

Punch grafts, minigrafts, and split skin grafts One RCT [51] assessed minipunch grafting plus PUVAsol versus split-skin grafting plus PUVAsol. One study [65] made a five-way comparison between autologous skin minigraft plus 8-methoxypsoralen, minigraft plus placebo, minigraft alone, 8-methoxypsoralen alone, and placebo alone. No outcomes of interest were addressed and no adverse effects were reported. One RCT [66] compared pigmentation spread resulting from the use of a topical corticosteroid (0.1% fluocinolone acetonide) after punch grafting versus PUVA therapy after punch grafting (see Topical corticosteroids section).

One systematic review was found [67], based on case series only (a total of 39 series, reporting on five different techniques). The highest success rates occurred with split-thickness grafting and suction blister epidermal grafting, with 87% of patients achieving >75% repigmentation (sample-size weighted averages; 95% CI, 82–91 and 83–90, respectively). With minigrafting, 68% of the patients (95% CI, 62–64) were successfully grafted. A trial comparing minigrafting and suction blister epidermal grafting [68] confirmed the results of the review, although the outcome measure was the proportion of patches rather than the proportion of patients.

In a placebo-controlled trial including 18 patients, the addition of a melanotropin analogue applied topically on minigrafted patches did not improve the success of the minigrafting [69].

Drawbacks Cobblestoning, superficial scarring, and variegated appearance were associated with the minipunch grafting group. In the split-skin grafting group, superficial scarring was observed in all cases, as also were hypertrophic scarring, depigmentation, tire-pattern appearance, milia formation, and rejection of grafts.

Melanocyte transplantation One RCT [70] assessed a technique involving transplantation of epidermal cell suspension obtained from a skin graft. No statistically significant difference was found between the groups with respect to the number of participants achieving greater than 75% repigmentation.

Drawbacks The only adverse effect reported [70] was one case of bacterial infection at the recipient site.

Comments/implications for practice The data on surgical procedures should be interpreted with caution, as they are derived mainly from small case series and only scarce comparative trials, with questionable designs and outcome measures.

Psychological therapy

One RCT [71] compared cognitive-behavioral therapy with person-centered therapy and also with controls receiving no psychological therapy. A total of 45 participants were enrolled. The study did not assess any other outcomes of interest.

Comments/implications for clinical practice Studies that take into account the effects of treatments on the patients' quality of life and global health, from the patient's point of view, are needed.

UNCORRECTED PROOFS

Key points

- A meta-analysis, one additional systematic review, and several subsequent RCTs showed that NB-UVB, psoralen plus UVA light (using sunlight or artificial light sources), and topical class 3 corticosteroids are effective in comparison with placebo in treating generalized and localized vitiligo.
- There is RCT evidence indicating that NB-UVB is at least as effective as PUVA in achieving repigmentation of treated lesions.
- RCTs have reported that concurrent topical calcipotriol potentiates the efficacy of PUVA, but not the efficacy UVB. However, the concurrent use of topical tacalcitol has been shown to increase the efficacy of NB-UVB.
- There is some RCT evidence that indicates that tacrolimus is as effective as topical clobetasol propionate in treating vitiligo, although no placebo-controlled trials were found. Evidence from one RCT indicates that topical pimecrolimus is not effective in treating vitiligo.
- There is scarce RCT evidence on the efficacy of melagenine, pseudocatalase, levamisole, and systemic antioxidant therapy.
- We found limited evidence of the effectiveness of surgical treatments for selected patients
- We found that treatments were evaluated mainly in the short term, with few comparative trials. The maintenance value of therapies and the assessment of patients' preferences, satisfaction, and quality of life have not yet been adequately addressed. Patient compliance is seldom reported in the studies.

References

1. Jacobson DL, Gange SJ, Rose NR, *et al*. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol* 1997;**84**(3):223–43.
2. Im S, Hann SK, Kim HI, *et al*. Biologic characteristics of cultured human vitiligo melanocytes. *Int J Dermatol* 1994;**33**(8):556–62.
3. Schallreuter KU, Wood JM. Free radical reduction in the human epidermis. *Free Radic Biol Med* 1989;**6**(5):519–32.
4. Morrone A, Picardo M, de Luca C, *et al*. Catecholamines and vitiligo. *Pigment Cell Res* 1992;**5**(2):65–9.
5. Grimes PE, Sevall JS, Vojdani A. Cytomegalovirus DNA identified in skin biopsy specimens of patients with vitiligo. *J Am Acad Dermatol* 1996;**35**(1):21–6.
6. Hann SK, Chun WH, Park YK. Clinical characteristics of progressive vitiligo. *Int J Dermatol* 1997;**36**(5):353–5.
7. Whitton ME, Pinart M, Batchelor J, *et al*. Interventions for vitiligo. *Cochrane Database Syst Rev* 2010;**1**:CD003263. doi: 10.1002/14651858.CD003263.pub4.
8. Matin R. Vitiligo in adults and children. *Clin Evid* 2011;**2011**:1717. Available at:: http://clinicalevidence.bmj.com/x/systematic-review/1717/interventions.html (accessed June 1, 2012).
9. Khalid M, Mujtaba G, Haroon T. Comparison of 0.05% clobetasol propionate cream and topical puvasol in childhood vitiligo. *Int J Dermatol* 1995;**34**(3): 203–5.
10. Lim-Ong M, Leveriza R, Ong B, *et al*. Comparison between narrow-band UVB with topical corticosteroid and narrow-band UVB with placebo in the treatment of vitiligo: a randomized controlled trial. *Philipp Dermatol Soc* 2005;**23**(14): 17–25.
11. Sassi F, Cazzaniga S, Tessari G, *et al*. Randomized controlled trial comparing the effectiveness of 308-nm excimer laser alone or in combination with topical hydrocortisone 17-butyrate cream in the treatment of vitiligo of the face and neck. *Br J Dermatol* 2008;**159**(5):1186–91.
12. Kumaran M, 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**(3):269–73.
13. Eryilmaz A, Seçkin D, Baba M. Pimecrolimus: a new choice in the treatment of vitiligo? *J Eur Acad Dermatol Venereol* 2009;**23**(11):1347–8.
14. Lepe V, Moncada B, Castanedo-Cazares JP, *et al*. A double-blind randomized trial of 0.1% tacrolimus vs 0.05% clobetasol for the treatment of childhood vitiligo. *Arch Dermatol* 2003;**139**(5):581–5.
15. Westerhof W, Nieuweboer-Krobotova L, Mulder PG, *et al*. Left-right comparison study of the combination of fluticasone propionate and UV-A vs. either fluticasone propionate or UV-A alone for the long-term treatment of vitiligo. *Arch Dermatol* 1999;**135**(9):1061–6.
16. Njoo MD, Spuls PI, Bos JD, *et al*. Nonsurgical repigmentation therapies in vitiligo. Meta-analysis of the literature. *Arch Dermatol* 1998;**134**(12):1532–40.
17. Bleehen SS. The treatment of vitiligo with topical corticosteroids. Light and electronmicroscopic studies. *Br J Dermatol* 1976;**94**(Suppl 12):43–50.
18. Koopmans-van Dorp B, Goedhart-van Dijjk B, Neering H, *et al*. Treatment of vitiligo by local application of betamethasone 17-valerate in a dimethyl sulfoxide cream base. *Dermatologica* 1973;**146**(5):310–4.
19. Kandil E. Treatment of vitiligo with 0.1% betamethasone 17-valerate in isopropyl alcohol – a double-blind trial. *Br J Dermatol* 1974;**91**(4):457–60.
20. Asilian A, Shabaram M, Faghihi G. Comparison of efficacy of conjugated estrogen cream 0.625% plus clobetasol 0.05% vs. clobetasol 0.05% alone in the treatment of vitiligo patients. *J Pak Assoc Derma* 2009;**19**:151–7.
21. Vasistha LK, Singh G. Vitiligo and intralesional steroids. *Indian J Med Res* 1979;**69**:308–11.
22. Parsad D, Saini R, Verma N. Combination of PUVAsol and topical calcipotriol in vitiligo. *Dermatology* 1998;**197**(2):167–70.
23. Ermis O, Alpsoy E, Cetin L, *et al*. Is the efficacy of psoralen plus ultraviolet A therapy for vitiligo enhanced by concurrent topical calcipotriol? A placebo-controlled double-blind study. *Br J Dermatol* 2001;**145**(3):472–5.
24. Lu-yan T, Wen-wen F, Lei-hong X, *et al*. Topical tacalcitol and 308-nm monochromatic excimer light: a synergistic combination for the treatment of vitiligo. *Photodermatol Photoimmunol Photomed* 2006;**22**(6):310–4.
25. Rodríguez-Martín M, García Bustínduy M, Sáez Rodríguez M, *et al*. Randomized, double-blind clinical trial to evaluate the efficacy of topical tacalcitol and sunlight exposure in the treatment of adult nonsegmental vitiligo. *Br J Dermatol* 2009;**160**(2):409–14.
26. Ada S, Sahin S, Boztepe G, *et al*. No additional effect of topical calcipotriol on narrow-band UVB phototherapy in patients with generalized vitiligo. *Photodermatol Photoimmunol Photomed* 2005;**21**(2):79–83.
27. Leone G, Pacifico A, Iacovelli P, *et al*. Tacalcitol and narrow-band phototherapy in patients with vitiligo. *Clin Exp Dermatol* 2006;**31**(2):200–5.
28. Kawalek AZ, Spencer JM, Phelps RG. Combined excimer laser and topical tacrolimus for the treatment of vitiligo: a pilot study. *Dermatol Surg* 2004;**30**(2): 130–5.
29. Passeron T, Ostovari N, Zakaria W, *et al*. Topical tacrolimus and the 308-nm excimer laser: a synergistic combination for the treatment of vitiligo. *Arch Dermatol* 2004;**140**(9):1065–9.
30. Esfandiarpour I, Ekhlasi A, Farajzadeh S, *et al*. The efficacy of pimecrolimus 1% cream plus narrow-band ultraviolet B in the treatment of vitiligo: a double-blind, placebo-controlled clinical trial. *J Dermatolog Treat* 2009;**20**(1):14–8.
31. Farajzadeh S, Daraei Z, Esfandiarpour I, *et al*. The efficacy of pimecrolimus 1% cream combined with microdermabrasion in the treatment of nonsegmental childhood vitiligo: a randomized placebo-controlled study. *Pediatr Dermatol* 2009; **26**(3):286–91.
32. Callen J, Chamlin S, Eichenfield LF, *et al*. A systematic review of the safety of topical therapies for atopic dermatitis. *Br J Dermatol* 2007;**156**(2):203–21.
33. Arellano FM, Wentworth CE, Arana A, *et al*. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. *J Invest Dermatol* 2007;**127**(4):808–16.
34. Procaccini E, Riccio G, Monfrecola G. Ineffectiveness of topical khellin in photochemotherapy of vitiligo. *J Dermatolog Treat* 1995;**6**(2):117–20.
35. Orecchia G, Perfetti L. Photochemotherapy with topical khellin and sunlight in vitiligo. *Dermatology* 1992;**184**(2):120–3.
36. Schallreuter KU, Moore J, Behrens-Williams S, *et al*. Rapid initiation of repigmentation in vitiligo with Dead Sea climatotherapy in combination with pseudocatalase (PC-KUS). *Int J Dermatol* 2002;**41**(8):482–7.
37. Sanclemente G, Garcia J, Zuleta J, *et al*. A double-blind, randomized trial of 0.05% betamethasone vs. topical catalase/dismutase superoxide in vitiligo. *J Eur Acad Dermatol Venereol* 2008;**22**(11):1359–64.
38. Souto M, Manhaes A, Milhomens C, *et al*. Comparative study between melagenina and placebo in the treatment of vitiligo. *An Bras Dermatol* 1997;**72**(3):237–9.
39. Parsad D, Pandhi R, Juneja A. Effectiveness of oral *Ginkgo biloba* in treating limited, slowly spreading vitiligo. *Clin Exp Dermatol* 2003;**28**(3):285–7.
40. Rath N, Kar HK, Sabhnani S. An open labeled, comparative clinical study on efficacy and tolerability of oral minipulse of steroid (OMP) alone, OMP with PUVA and broad/narrow band UVB phototherapy in progressive vitiligo. *Indian J Dermatol Venereol Leprol* 2008;**74**(4):357–60.
41. Radmanesh M, Saedi K. The efficacy of combined PUVA and low-dose azathioprine for early and enhanced repigmentation in vitiligo patients. *J Dermatolog Treat* 2006;**17**(3):151–3.
42. Dell'Anna ML, Mastrofrancesco A, Sala R, *et al*. Antioxidants and narrow band-UVB in the treatment of vitiligo: a double-blind placebo controlled trial. *Clin Exp Dermatol* 2007;**32**(6):631–6.
43. Middelkamp-Hup M, Bos J, Rius-Diaz F, *et al*. Treatment of vitiligo vulgaris with narrow-band UVB and oral *Polypodium leucotomos* extract: a randomized

UNCORRECTED PROOF

double-blind placebo-controlled study. *J Eur Acad Dermatol Venereol* 2007;**21**(7):942–50.

44. Agarwal S, Ramam M, Sharma VK, *et al.* A randomized placebo-controlled double-blind study of levamisole in the treatment of limited and slowly spreading vitiligo. *Br J Dermatol* 2005;**153**(1):163–6.
45. Siddiqui AH, Stolk LM, Bhaggoe R, *et al.* L-Phenylalanine and UVA irradiation in the treatment of vitiligo. *Dermatology* 1994;**188**(3):215–8.
46. Tjioe M, Gerritsen MJP, Juhlin L, *et al.* Treatment of vitiligo vulgaris with narrow band UVB (311 nm) for one year and the effect of addition of folic acid and vitamin B12. *Acta Derm Venereol* 2002;**82**(5):369–72.
47. Bhatnagar A, Kanwar AJ, Parsad D, *et al.* Comparison of systemic PUVA and NB-UVB in the treatment of vitiligo: an open prospective study. *J Eur Acad Dermatol Venereol* 2007;**21**(5):638–42.
48. Pathak MA, Mosher DB, Fitzpatrick TB. Safety and therapeutic effectiveness of 8-methoxypsoralen, 4,5′,8-trimethylpsoralen, and psoralen in vitiligo. *Natl Cancer Inst Monogr* 1984;**66**:165–73.
49. Ruiz Maldonado R, Tamayo Sanchez L. 4-5-8 Trimethylpsoralen in vitiligo. Controlled study of its therapeutic and toxic effect in children. *Actas Dermosifiliogr* 1975;**66**(9–10):513–26 (in Spanish).
50. Farah F, Kurban A, Chaglassian H. The treatment of vitiligo with psoralens and triamcinoline by mouth. *Br J Dermatol* 1967;**79**(2):89–91.
51. Khandpur S, Sharma VK, Manchanda Y. Comparison of minipunch grafting versus split-skin grafting in chronic stable vitiligo. *Dermatol Surg* 2005;**31**(4):436–41.
52. Asawanonda P, Kijluakiat J, Korkij W, *et al.* Targeted broadband ultraviolet b phototherapy produces similar responses to targeted narrowband ultraviolet B phototherapy for vitiligo: a randomized, double-blind study. *Acta Derm Venereol* 2008;**88**(4):376–81.
53. Casacci M, Thomas P, Pacifico A, *et al.* Comparison between 308-nm monochromatic excimer light and narrowband UVB phototherapy (311–313 nm) in the treatment of vitiligo – a multicentre controlled study. *J Eur Acad Dermatol Venereol* 2007;**21**(7):956–63.
54. Anbar TS, Westerhof W, Abdel-Rahman AT, *et al.* Effect of one session of ER:YAG laser ablation plus topical 5fluorouracil on the outcome of short-term NB-UVB phototherapy in the treatment of non-segmental vitiligo: a left-right comparative study. *Photodermatol Photoimmunol Photomed* 2008;**24**(6):322–9.
55. Yuksel EP, Aydin F, Senturk N, *et al.* Comparison of the efficacy of narrow band ultraviolet B and narrow band ultraviolet B plus topical catalase–superoxide dismutase treatment in vitiligo patients. *Eur J Dermatol* 2009;**19**(4):341–4.
56. Bakis-Petsoglou S, Le Guay JL, Wittal R. A randomized, double-blinded, placebo-controlled trial of pseudocatalase cream and narrowband ultraviolet B in the treatment of vitiligo. *Br J Dermatol* 2009;**161**(4):910–7.
57. Stinco G, Piccirillo F, Forcione M, *et al.* An open randomized study to compare narrow band UVB, topical pimecrolimus and topical tacrolimus in the treatment of vitiligo. *Eur J Dermatol* 2009;**19**(6):588–93.
58. Asawanonda P, Klahan S-O. Tetrahydrocurcuminoid cream plus targeted narrowband UVB phototherapy for vitiligo: a preliminary randomized controlled study. *Photomed Laser Surg* 2010;**28**(5):679–84.
59. Westerhof W, Nieuweboer-Krobotova L. Treatment of vitiligo with UV-B radiation vs topical psoralen plus UV-A. *Arch Dermatol* 1997;**133**(12):1525–8.
60. Hofer A, Hassan AS, Legat FJ, *et al.* Optimal weekly frequency of 308-nm excimer laser treatment in vitiligo patients. *Br J Dermatol* 2005;**152**(5):981–5.
61. Goldinger SM, Dummer R, Schmid P, *et al.* Combination of 308-nm xenon chloride excimer laser and topical calcipotriol in vitiligo. *J Eur Acad Dermatol Venereol* 2007;**21**(4):504–8.
62. Hui-Lan Y, Xiao-Yan H, Jian-Yong F, *et al.* Combination of 308-nm excimer laser with topical pimecrolimus for the treatment of childhood vitiligo. *Pediatr Dermatol* 2009;**26**(3):354–6.
63. Ozdemir M, Cetinkale O, Wolf R, *et al.* Comparison of two surgical approaches for treating vitiligo: a preliminary study. *Int J Dermatol* 2002;**41**(3):135–8.
64. Czajkowski R. Comparison of melanocytes transplantation methods for the treatment of vitiligo. *Dermatol Surg* 2004;**30**(11):1400–5.
65. Navarro J, Canales A, Salado Ponce H. Autologous skin minigraft and ingestion of 8-methoxypsoralen in patients with stable vitiligo vulgaris. *Dermatologia Rev Mex* 2002;**46**:260–7.
66. Barman KD, Khaitan BK, Verma KK. A comparative study of punch grafting followed by topical corticosteroid versus punch grafting followed by PUVA therapy in stable vitiligo. *Dermatol Surg* 2004;**30**(1):49–53.
67. Njoo MD, Westerhof W, Bos JD, *et al.* A systematic review of autologous transplantation methods in vitiligo. *Arch Dermatol* 1998;**134**(12):1543–9.
68. Gupta S, Jain VK, Saraswat PK. Suction blister epidermal grafting versus punch skin grafting in recalcitrant and stable vitiligo. *Dermatol Surg* 1999;**25**(12):955–8.
69. Schwartzmann-Solon AM, Visconti MA, Castrucci AM. Topical application of a melanotropin analogue to vulgar vitiligo dermo-epidermal minigrafts. *Braz J Med Biol Res* 1998;**31**(12):1557–64.
70. Tegta GR, Parsad D, Majumdar S, *et al.* Efficacy of autologous transplantation of noncultured epidermal suspension in two different dilutions in the treatment of vitiligo. *Int J Dermatol* 2006;**45**(2):106–10.
71. Papadopoulos L, Walker C, Anthis L. Living with vitiligo: a controlled investigation into the effects of group cognitive-behavioural and person-centred therapies. *Dermatol Psychosom* 2004;**5**(4):172–7.

UNCORRECTED PROOFS