Vitiligo

A guide to diagnosis and management for GPs

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GPs are ideally placed to make the diagnosis of vitiligo. It is a treatable autoimmune condition that is best managed by a multidisciplinary team.

KEY POINTS

- Vitiligo is a chronic and relapsing autoimmune condition for which treatment should be offered.
- The diagnosis of vitiligo should be considered in children and adults who present with acquired depigmented patches of skin, mucosa or hair.
- Thyroid function should be tested in all patients with vitiligo.
- GPs may play a key role in identifying patients dealing with the psychosocial burden of vitiligo and can discuss management options with them.

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Vitiligo is an acquired depigmenting cutaneous disorder in which pigment cells (melanocytes) are destroyed by autoreactive T cells in the immune system. This results in characteristic white patches that can involve skin (leukoderma), hair (leukotrichia), mucosa and even the retina. The contrast between depigmented skin and normal skin can be disfiguring and have a profound impact on quality of life in both adults and children. Low self-esteem, isolation and stigmatisation are some of the many psychological manifestations reported by patients with vitiligo.[1]

Most patients in Australia initially present to their primary healthcare provider for diagnosis and management advice. GPs are in a position to diagnose obvious cases of vitiligo, order appropriate screening investigations, commence simple topical therapy and refer the patient to a dermatologist early in the disease to enhance disease outcomes. GPs should also broach and address any accompanying psychological consequences of this devastating condition and recommend ongoing psychosocial support.

Epidemiology

Vitiligo is one of the most common cutaneous disorders of depigmentation with an estimated worldwide prevalence of up to 2%.[2] Vitiligo affects all races and does not have a sex predilection. Vitiligo can appear at any age but 50% of those affected experience pigment loss before the age of 20 years and about 80% note depigmentation before the age of 30 years.[3] The disease course can be unpredictable with variable severity.

KEY CLINICAL HISTORY POINTS IN THE DIAGNOSIS OF VITILIGO

- Age of onset of noticing depigmented patches
- Triggers preceding depigmentation
- Symptoms
- Progression of depigmentation
- Concomitant diseases
- History of or comorbid autoimmune disorders, such as thyroid dysfunction
- Medications (including over-the-counter preparations and herbal remedies)
- Occupational history – trauma, inciting chemical or topical exposure
- Family history of vitiligo or autoimmune disorder
- Impact on activities of daily living
- Symptoms of depression or anxiety
- Desire and motivation to seek treatment

Many patients are understandably anxious about the profound discolouration, especially when exposed areas of skin are affected or when the disease becomes more generalised. Early and prompt recognition of vitiligo, commencing first-line therapy and initiating early referral lead to improved rates of repigmentation and patient outcomes.[4,5]

Aetiology

The pathogenesis of vitiligo incorporates intrinsic defects within melanocytes that can activate cellular stress responses and autoimmune mechanisms. The aetiology involves an interplay between genetic and environmental risks that initiates the autoimmune destruction of melanocytes in skin.[6] Intrinsic melanocyte defects, in addition to autoimmune destruction of melanocytes in skin, result in cutaneous depigmentation.[6]

Patients with vitiligo have increased numbers of autoreactive melanocyte-specific CD8+ T cells in their skin and blood; these T cells are directly responsible for melanocyte destruction and their levels correlate with disease severity.[7] CD8+ T cells are major producers of the cytokine interferon-gamma (IFNγ).[7] Studies investigating gene expression profiling have shown increased expression of IFNγ and IFNγ-induced genes in the lesional skin of patients with vitiligo.[8] Importantly, levels of C-X-C motif chemokine ligand 10 (CXCL10), an IFNγ-induced chemokine, have also been found to be elevated in the serum of patients with vitiligo.[9] The IFNγ–CXCL10 pathway induces vitiligo, with cytotoxic autoreactive CD8+ T cells and CD4+ regulatory T cells playing an important role in this disease.[8,9]

Genetics

Studies indicate a non-Mendelian, polygenic inheritance pattern of vitiligo affecting individuals from multiple lines of the same family, with up to 50% of affected individuals having affected relatives.[10] The risk of a patient's sibling developing the disease is 6% and for an identical twin it is 23%.[11] Patients with vitiligo and their relatives also have an increased risk of developing other autoimmune diseases.[11]

Autoimmunity

The frequency of comorbid autoimmune diseases, such as Addison's disease, thyroid disease, alopecia areata, psoriasis, type 1 diabetes, rheumatoid arthritis, inflammatory bowel disease and systemic lupus erythematosus is significantly elevated in patients with vitiligo and their first-degree relatives.[11] An increased frequency of organ-specific autoantibodies has been reported in patients with vitiligo.[12,13] Additionally, the presence of antibodies to surface and cytoplasmic melanocyte antigens, which are capable of inducing destruction of melanocytes grown in culture, further supports an autoimmune pathogenesis of the disease.[14]

Oxidative stress

Oxidative stress may also contribute to melanocyte destruction in susceptible individuals via activation of the innate immune response.[15] Reactive oxygen species are capable of activating receptors to initiate inflammation.[16] Depletion of antioxidants has been demonstrated in patients with vitiligo.[16]

The GP consultation

Diagnosing vitiligo relies on a combination of meticulous history taking (Box) and clinical examination (Table 1). The type and severity of vitiligo should be established, as well as time spent assessing the psychological impact of the condition. Laboratory investigations may assist in identifying any possible underlying autoimmune comorbidity. Histopathological tissue analysis is seldom required; however, it can be helpful if the clinical features are uncertain. Histopathology results may also be equivocal, requiring consultation with a dermatologist.

History

Past and current medication history can be helpful. Past history of treatment with tyrosine kinase inhibitors such as gefitinib (typically used to treat non-small cell lung cancers and solid tumours of the head and neck such as squamous cell carcinoma of the parotid) or imatinib (typically used to treat leukaemia) has been reported to result in depigmentation.[17] Similarly, vitiligo has been reported in patients after using imiquimod 5% cream for the treatment of condylomata acuminata.[18]

Biologic drugs such as BRAF inhibitors, IFN-α2b and anti-MEK-MAP kinase drugs have also been implicated in the

TABLE 1. CLINICAL EXAMINATION FINDINGS OF VITILIGO

Type of vitiligo	Features
Segmental	
Blaschkoid	• Depigmentation along a line of blaschko
Nonsegmental	
Generalised	• Bilateral, often symmetric, depigmented macules or patches • Random distribution over multiple anatomical sites • Commonly affected regions include sites of pressure, friction or trauma
Acrofacial/acral	• Depigmented macules confined to the distal extremities and/face • Can transform into the generalised form
Mucosal	• Depigmentation involving the oral or genital mucosa
Universal	• Complete or nearly complete depigmentation of the skin • Hair may be spared

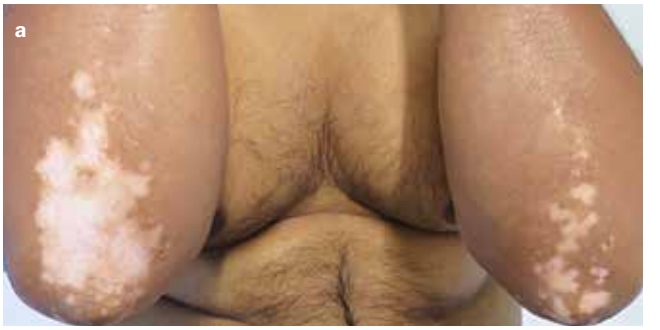
development of vitiligo.[19] The presence of vitiligo in patients with melanoma is thought to be a marker of an immune response against the tumour and may be an indicator of a favourable prognosis in advanced disease.[20] Vitiligo lesions in untreated patients and patients treated with biologic therapy or IFN-α2b were found to be associated with improved survival rates in patients with metastatic melanoma.[21]

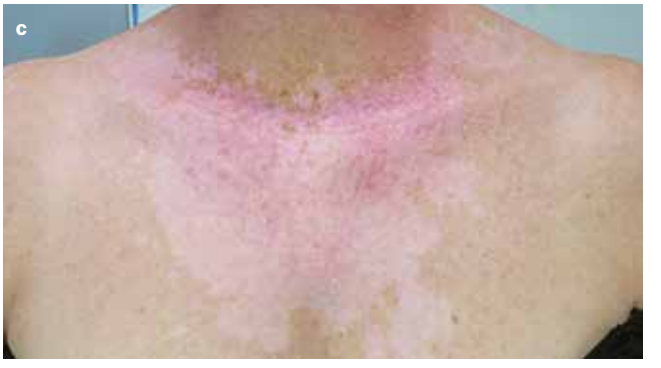
Taking a medication history is also helpful in identifying what treatments, if any, the patient has tried in the past and how successful they were. This can help direct and individualise future vitiligo treatment.

Vitiligo is often a diagnosis that weighs heavily on the psyche of the patient, especially when affected areas cannot be effectively camouflaged. The disfiguring depigmentation can have a major impact on the patient's self-esteem with the emotional burden exerting a tremendous psychological effect, especially in people with skin of colour. It is therefore crucial for the clinician to assess the impact of vitiligo on the patient's quality of life and provide psychosocial support and counselling when needed.

Clinical examination

In patients with light skin, depigmentation may be difficult to appreciate and changes may only be first noticed during warmer months when the rest of the skin becomes tanned. A Wood's lamp (365 nm ultraviolet [UV] A light) can be helpful in revealing depigmentation, which is accentuated with fluorescence.





Figures 1a to c. Vitiligo on the elbows (a, top) and hands (b, right) of an Indian man, and on the chest and neck of a Caucasian woman (c, bottom).

Physical examination

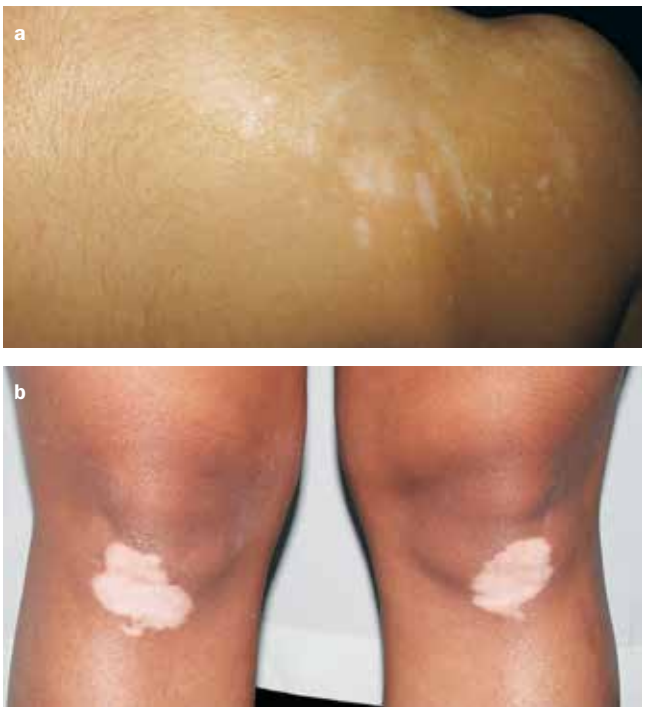
Vitiligo is characterised by acquired, symmetrical, discrete, well-demarcated, asymptomatic, irregularly shaped depigmented macules that may affect skin, mucosa and hair (Figures 1a to c).

Given the potential subtle nature of vitiligo lesions, especially in sun-protected areas, a full body skin examination should be performed to assess the extent of disease. Clinical examination can be assisted with a Wood's light (Figure 2), especially in individuals with lighter skin types. A Wood's light examination can accentuate well-demarcated depigmented skin where a bright blue-white fluorescence is emitted. Meticulous examination should be devoted to areas such as the ocular orifice, mouth, umbilicus, nipples and anogenital regions, as well as regions of

Figure 2. Wood's light examination of vitiligo on the scalp, neck and back.

skin folds such as the fingers, axillae, inguinal areas, elbows and knees. A systematic approach to a full body skin examination, starting at the scalp and hair, is recommended to avoid missing discrete lesions.

Patients may have vitiligo lesions in areas of cutaneous trauma including friction, pressure, cuts and abrasions. This is termed the Koebner phenomenon (Figures 3a and b). Halo naevi have been identified in a small portion of children with nonsegmental vitiligo and may be an indicator of the development of generalised vitiligo.[22] Although most patients with vitiligo are affected in different areas of their body, a minority develop the segmental variant of vitiligo in which a patch of depigmentation is noted in a pattern that correlates with other mosaic skin disorders.



Figures 3a and b. Koebnerisation with linear depigmentation on the back (a, top) and Koebnerisation on the knees (b, bottom) of a young boy.

Scale, textural change and anaesthetic areas of skin are all clues to diagnoses other than vitiligo (see the differential diagnoses section below).

Examination for signs of systemic autoimmune or inflammatory diseases, including thyroid and connective tissue diseases, are important in the overall clinical assessment of a patient with vitiligo.

Investigations

Serology

The strong association of vitiligo with autoimmune thyroid disorders warrants screening of thyroid function (Flowchart). In a cross-sectional comparative study, thyroid dysfunction, serum thyroid-stimulating hormone (TSH) abnormalities and anti-thyroid peroxidase (TPO) antibody positivity were more common in the group with vitiligo compared with the control group.[23] Furthermore, a recent systematic review found that thyroid disease, autoimmune thyroid disease and the presence of thyroid-specific autoantibodies showed a mean prevalence of 15.1%, 14.3% and 20.8%, respectively, in people with vitiligo.[24]

A family history or clinical examination findings suggestive of other autoimmune disorders may warrant assay testing of additional relevant antibodies.

Histopathology

Skin biopsies are not routinely required in patients with vitiligo because it is usually a clinical diagnosis. In hypopigmented skin of uncertain aetiology, a skin biopsy may be helpful. The skin biopsy (preferably a punch biopsy) should encompass the border of the depigmented patch and surrounding unaffected skin. It is necessary to include normal skin and lesional skin in the one biopsy because it provides a 'normal skin' comparison for the pathologist. It also provides the crucial 'edge of the lesion' where the inflammatory cell infiltrate can be seen.

Histopathology of the skin from a patient with vitiligo typically reveals a loss of melanin pigment in the epidermis and an absence of melanocytes.[22] Occasional lymphocytes that can be highlighted as CD8+ T cells can also be observed at the advancing border of depigmented skin, along with vacuolar degeneration of basal keratinocytes, spongiosis and a lymphohistiocytic infiltrate at the dermo-epidermal junction.[25]

Differential diagnoses

Most of the differential diagnoses of vitiligo present with hypopigmentation rather than depigmentation. These are listed in Table 2.

Management

Management options for patients with vitiligo have changed over the past few decades and recent research has provided insight into new possible treatment options.

Informing the patient that vitiligo is an autoimmune condition that can potentially be psychologically devastating and that treatment is available is the first step in validating the patient's concerns and improving patient outcomes. Treatment goals for vitiligo should be guided by the patient, their age, their skin type, the location of the affected skin and hair, the extent of disease and the impact on the patient's quality of life. Communication between the GP, psychologist, counsellor and dermatologist is crucial in order to facilitate an individualised treatment plan and to set realistic expectations.

The goal of treatment is to halt disease progression, assist with repigmentation and then maintain that repigmentation over time, while simultaneously providing psychological support.

Photoprotection

General photoprotective advice can help in minimising the profound colour difference between normal skin that pigments and vitiliginous skin that does not. Photoprotection involves:

- avoiding peak UV light periods from 11 am to 3 pm
- applying sunscreen 15 to 30 minutes before sun exposure
- reapplying sunscreen every two hours and after towel drying activities.

The risk of skin cancer in patients with vitiligo however, appears to be lower than in matched controls.[26]

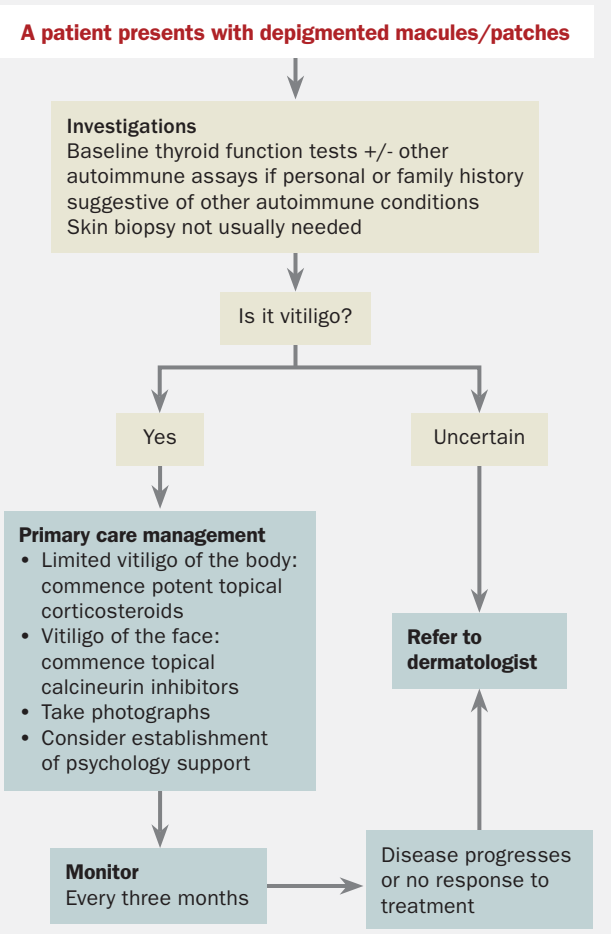
Cosmetic camouflage

Cosmetic camouflage can be beneficial for patients with vitiligo that affects exposed areas. Products include foundation-based cosmetics and topical tanning products containing dihydroxyacetone (DHA), which can have a longer lasting stay-on effect. Colour matching can be challenging and costly but worth trialling for cosmetically sensitive areas of skin. Tattooing should be avoided given the risk for koebnerisation and oxidation of tattoo pigment causing further dyschromia.

As part of education and management, GPs could direct patients to camouflaging services that may assist in disguising the disfiguring depigmentation. Camouflaging services and techniques should not be underestimated given the tremendous psychosocial impact that vitiligo can have on the lives of those affected.

With the unpredictable disease course and possible cutaneous side effects of vitiligo, treatment initiation and regular monitoring should be undertaken in a multidisciplinary team setting. This should involve the GP, psychologist, psychiatrist and dermatologist, in addition to other relevant physicians such as endocrinologists.

INVESTIGATION AND MANAGEMENT OF A PATIENT WITH VITILIGO



Topical treatments

Repigmentation has been demonstrated with the use of potent topical corticosteroids.[27] There is currently no evidence demonstrating the optimal duration of treatment with topical corticosteroids. Side effects of topical corticosteroids include skin atrophy, telangiectasia, acneiform eruptions and hypertrichosis; however, the risk of side effects is minimal when these drugs are used according to recommended guidelines.[28] Potent topical corticosteroids can induce hypopigmentation at the site of application. For these reasons, the use of topical corticosteroids on vitiliginous skin on the head and neck is not ideal.

For limited vitiligo affecting body sites, potent topical corticosteroids (i.e. mometasone furoate and betamethasone dipropionate) can be used as first-line treatment, applied daily in a cyclical fashion with 'steroid-free' weeks.

Topical calcineurin inhibitors, such as tacrolimus (off-label use), are first-line treatments for patients with vitiligo that affects

TABLE 2. DIFFERENTIAL DIAGNOSES OF ACQUIRED DEPIGMENTED OR HYPOPIGMENTED SKIN DISORDERS

Differential diagnosis	Presentation
Pityriasis alba	• Hypopigmented mildly scaly patches commonly on sun-exposed sites • Patches can be pruritic and improve with low-potency topical corticosteroids
Pityriasis versicolor	• Hypopigmented macules and patches over upper trunk, back and chest with fine dry surface scale • Golden yellow fluorescence under Wood's light
Naevus depigmentosus	• Circumscribed segmental area of hypopigmentation present from birth or detected in first year of life • Little or no change over time
Idiopathic guttate hypomelanosis	• Multiple small porcelain-white macules on sun-exposed areas (e.g. limbs) • Seen in up to 80% of patients over the age of 70 years • Biopsy shows reduced number of melanocytes
Progressive macular hypomelanosis	• Nonscaling hypopigmented patches on trunk (especially lower back) caused by *Propionibacterium acnes* • Typically affects young patients
Hypopigmented mycosis fungoides (T cell lymphoma)	• Widespread hypopigmented, scaly patches with atrophy in bathing trunk distribution, especially in those with skin of colour
Leprosy	• Ill-defined hypopigmented macules or patches with diminished sensation, possible hair loss, skin atrophy and absent sweating in affected skin

the head and neck.[29] These preparations are available at compounding pharmacies in Australia, at a concentration of either 0.03% or 0.1%, which is mixed with an aqueous cream or ointment base. The topical preparation is applied once or twice daily and may result in gradual repigmentation. However, if the vitiligo lesions are widespread then it is best to refer the patient to a dermatologist to consider a combination of phototherapy and topical therapy, with ongoing monitoring for cutaneous side effects and efficacy.

Narrow-band UVB phototherapy

There is evidence to show that narrow-band UVB phototherapy may be able to stabilise active vitiligo. It is considered first-line treatment for patients with generalised vitiligo.[29] However, targeted phototherapy may also be delivered depending on the accessibility and location of the vitiligious skin. Patients should receive phototherapy two to three times per week. No studies have been performed to determine how long phototherapy should be used but patient tolerability and response are two factors taken into consideration when assessing whether further treatment should be prescribed. Ideally, patients should be assessed every 12 weeks when undergoing phototherapy to evaluate response and occurrence of potential cutaneous side effects.

Oral corticosteroids

Some studies suggest that rapidly progressive and aggressive vitiligo may be stabilised with systemic immunosuppression with pulsed low-dose oral corticosteroids. Although prospective, randomised trials are lacking, mini-pulse therapy with oral dexamethasone 2.5 mg on two consecutive days weekly for an average of three months may be helpful for a select group of patients with vitiligo.[30]

It is important, however, to deliver this therapy for no more than 12 weeks and only to patients with no contraindications. It is also crucial to evaluate the patient for short- and long-term side effects of oral corticosteroid use.

Psychosocial support

The extent of vitiligo disease may not always correlate with psychological morbidity experienced by patients.[31] Facial involvement of vitiligo, even if small, can have a remarkable effect on patient's self-esteem. All clinicians should spend time listening and empathising with affected patients.

In some darker-skinned populations, the patient may feel a loss of ethnic identity and may even be stigmatised because of a misunderstanding that vitiligo is infectious. Affected patients may have fears about acceptance and feel socially and culturally isolated.[32] Cumulatively, this can contribute to the overall burden the patient may already be experiencing. It is also important to note that such feelings may arise with recurrence and progression of vitiligo.[32]

As well as initiating diagnosis and treatment, GPs play a pivotal role in assessing and addressing the psychosocial ramifications of vitiligo. Coping styles differ between individuals

and it is important for patients to find and develop coping mechanisms that suit their personality, culture and psychosocial experience. Although medical consultations may be limited, dedicating meaningful time to listen and hear patient concerns can direct management in offering the most appropriate treatment, therapeutic alternatives and referral to patient support groups and local counselling services. Some helpful patient resources include the Global Vitiligo Foundation (www.vitiligoworkinggroup.com) and the Vitiligo Association of Australia (www.http://vitiligo.org.au).

Surgical therapies

Surgical therapies such as punch and blister grafting and non-cultured epidermal cell grafting can be used to repigment recalcitrant yet stable vitiligo in patients who are able to tolerate the procedure, local anaesthetic and laser surgery.

Depigmenting creams

Monobenzyl ether of hydroquinone (MBEH) has been trialled for use as a depigmenting agent for patients with extensive vitiligo. MBEH can cause permanent destruction of melanocytes and induces depigmentation not only at the application site but also in other remote body areas.[33] Its use is therefore only recommended when complete depigmentation is desired in a patient with vitiligo involving more than 70% body surface area.[33]

Potential side effects of MBEH include irritant contact dermatitis, pruritus, severe xerosis and even alopecia. Prior counselling about the permanent nature of the depigmenting treatment and change in appearance, and the patient's expectations is required before embarking on therapy.

Laser therapy

Excimer laser utilises xenon-chlorine gas that produces a monochromatic laser light (308 nm wavelength) to cause repigmentation. Research has shown swifter repigmentation with this device compared with phototherapy.[34] Also, it is easier to use on small areas of involvement without having to expose the entire body to the light source but results are variable.[34] Furthermore, laser may not be suitable for all patients, and the financial burden of a lengthy treatment phase (treatment may need to be continued for many months or even up to one year) should be considered.

Vitamin D analogues

Evidence supporting sunlight exposure and the use of vitamin D analogues in patients with vitiligo remains inconclusive. The basis for the use of vitamin D analogues such as calcipotriol stems from evidence showing that receptors known as 1-alpha-hydroxyvitamin D3 can stimulate melanogenesis.[35] Vitamin D analogues have been used in combination with UV light and topical corticosteroids with variable results.[36,37]

Complementary therapies

There is limited evidence from high-quality studies to support the use of antioxidants and vitamins for the treatment of patients with vitiligo.

Future directions

With the recent advances in our understanding of the pathogenesis of vitiligo, scientific investigations of new treatment options under specialist guidance are underway.

Janus kinase (JAK) enzymes are important signals that can direct immune cells. Antibody neutralisation of IFN or CXCL10 has been shown to reverse depigmentation.[8] It has been proposed that because IFNγ signal transduction occurs through the JAK 1/2 pathway, the use of JAK inhibitors such as tofacitinib (JAK 1/3 inhibitor) or ruxolitinib (JAK 1/2 inhibitor) can lead to a blockade of IFNγ signalling and downstream CXCL10 expression.[8,38] With this, it is plausible to reason that repigmentation in patients with vitiligo is possible and this has been demonstrated in case reports.[39,40] Further clinical trials of biologics are now underway and will undoubtedly unveil new and promising treatments.

Conclusion

Vitiligo is a treatable, autoimmune condition best managed by a multidisciplinary team. Good communication is vital to address patient concerns, dispel myths and guide meaningful management. GPs play a crucial role in promptly diagnosing the condition, investigating the coexistence of other autoimmune conditions, addressing the psychosocial impact of the condition and promptly commencing first-line topical therapies. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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