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A problem shared ...

'When it is obvious that the goals cannot be reached, don't adjust the goals, adjust the action steps.'
Confucius

CHAD J. SHAFFER/GETTY

■ Having colleagues on hand to help advise on diagnosis and treatment is an invaluable asset for a dermatologist to have in the workplace

When I came to work in Lincolnshire 16 years ago, initially as a single-handed consultant, I had two principal concerns. First, what would I do when I did not know the diagnosis? Second, how I would cope with those patients with chronic, intractable dermatoses – patients with nodular prurigo, palmoplanter pustulosis, difficult atopic eczema, or severe psoriasis? I felt much better about the first group after recalling the kind and wise words of the great Dr John Savin, who taught me as a Senior Registrar in Edinburgh. I had just finished my final dermatology clinic before leaving to become a consultant. I, somewhat ruefully, remarked, 'I've just done my last clinic and I haven't got a clue what was wrong with four of the patients'. Dr Savin responded along the lines of, 'Don't worry, I've been doing dermatology for over 30 years and it keeps happening to me – that's the fascination of dermatology!' Well, after 20 years of practising dermatology, the fascination persists!

The second group of patients pose a different problem. I feel a mixture of inadequacy and frustration that I am unable to 'cure' them or, at least, relieve their symptoms effectively. Aligned to this is a sneaking fear that I may not have made the correct diagnosis. These patients, who I generally refer to as my 'old friends', muddle along with me as we try one partially-effective treatment after another – often wondering if any improvement we find is simply an observation of their condition remitting spontaneously – that is, regressing to the mean.

The most valuable asset here is working as a team. The old adage that 'a problem shared is a problem halved' is certainly true. I have worked in a team of dermatologists in Lincolnshire for over ten years and I would be very reluctant to venture out alone again. The availability of colleagues to pop in to the consulting room, so we can see patients together, is invaluable. While I enjoy the relative peace and quiet of my clinics in the rural community hospitals, where I am often working on my own, I have the constant reassurance of knowing that the patients can come along to the combined clinic that we hold in Lincoln every month, so they can see a 'proper' dermatologist.

My work programme changed a few months ago, reducing the number of my weekly clinics from seven down to four, as I took up some administrative tasks as a part-time deputy medical director. Some of the patients I had been looking after, intermittently, for many years turned up in my colleagues' clinics and then found their way to the combined clinic. So, on a recent Thursday afternoon, we listened to the patients' stories, examined them together and formulated a treatment plan for the next few months – as doctors do. The real value was in the support we derived from each other, together with the reassurance it gave to our patients.

With the advent of clinical commissioning groups, the advent of modern technology and the move to managing more patients in the community, we need to work together to provide this support more readily across the whole healthcare community. Our challenge is how to bring it about.

Neill Hepburn, Editor

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DERMATOLOGY IN PRACTICE 2013; Vol 19 No 1

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Hydroxychloroquine use in treating skin diseases

Antimalarials are used by dermatologists to treat various skin conditions (see Table 1). Since the 1950s, the 4-aminoquinolone derivative of quinine, hydroxychloroquine, has been widely used in dermatology, in preference to chloroquine. Compared with other immunosuppressant medications used to treat inflammatory skin conditions, hydroxychloroquine is considered safer with a more favourable side-effect profile. This article aims to summarise the uses and adverse effects of hydroxychloroquine and the monitoring of dermatological patients prescribed the drug.

Indications for use

Lupus erythematosus

Hydroxychloroquine is considered first-line systemic therapy in most cutaneous forms of lupus. According to a 1963 review, discoid lupus erythematosus (LE) responded so favourably to chloroquine that 'double-blind studies were not required',[1] and a non-randomised double blind trial of hydroxychloroquine versus placebo demonstrated significant responses at three months, persisting for one year.[2] Large open clinical trials have demonstrated benefit of hydroxychloroquine in chronic and subacute cutaneous LE.[3,4] Lupus tumidus and lupus panniculitis are reported to improve with hydroxychloroquine.[5,6] Verrucous, or hypertrophic, plaques are less responsive.

Treatment also improves non-specific features in patients with systemic LE (SLE), such as lethargy/fatigue, arthralgia/myalgia, serositis, mucous membrane ulceration, calcinosis cutis and photosensitivity.[7] The number of flare-ups in SLE is reduced and improved overall survival rates have been reported.[8,9] Antimalarials also appear to lower lipid levels in SLE, suggesting a further cardioprotective role, in addition to lowering rates of thrombosis.[10]

The standard dose of hydroxychloroquine for cutaneous LE is 200–400 mg daily.[11] In some cases, doctors prescribe a loading dose and then reduce to a lower maintenance dose. It is also often used in combination with mepacrine (quinacrine), another antimalarial drug, when patients are unresponsive to hydroxychloroquine alone. It is well recognised that smoking inhibits the therapeutic effect, and patients must be counselled regarding this prior to starting the medication.[12]

Table 1. Clinical uses of hydroxychloroquine

Group	Dermatological condition
Connective tissue diseases	Lupus erythematosus • Systemic • Subacute cutaneous • Discoid • Tumidus • Panniculitis Sjogren's syndrome Scleroderma
Granulomatous skin conditions	Cutaneous sarcoidosis Granuloma annulare Necrobiosis lipoidica
Photodermatoses	Polymorphic light eruption Porphyria cutanea tarda Solar urticaria
Hair disorders	Lichen planopilaris Frontal fibrosing alopecia
Genodermatoses	Epidermolysis bullosa
Other	Urticarial vasculitis Eosinophilic fasciitis Chronic ulcerative stomatitis Reticular erythematous mucinosis

Polymorphic light eruption

Polymorphic light eruption is a photodermatosis that mostly occurs in young women. It is characterised by itchy skin lesions of variable morphology, occurring mostly in spring or early summer on sun-exposed body sites. The pathogenesis may involve resistance to ultraviolet light radiation-induced immunosuppression. Although hydroxychloroquine is not considered first-line treatment, two controlled efficacy trials[13,14] have reported increased sun tolerance, moderate clinical improvement and a significant reduction in rash with hydroxychloroquine. The recommendation is that in the event of failure of first-line treatments or contraindications, hydroxychloroquine can be given at a dose of 200–400 mg daily, prior to attempting an increase in sun exposure.

Porphyria cutanea tarda

Porphyria cutanea tarda (PCT) is characterised by photosensitivity, with skin blistering and scarring following exposure to sunlight. The primary

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cause is a deficiency of uroporphyrinogen decarboxylase, an enzyme in the heme synthesis pathway. This can occur as a result of inherited deficiency of the enzyme, although a number of risk factors can both cause and exacerbate the symptoms of the disease; for example, excess alcohol intake and hepatitis C. Management includes reduction of excess iron through repeated phlebotomy. Low-dose hydroxychloroquine (100 mg twice weekly) is used to achieve long-term remission of disease, with dose adjustments according to clinical response. In patients with PCT, antimalarials are reported to cause an acute hepatitis, so regular liver function test monitoring should be undertaken.

Cutaneous sarcoidosis

For cutaneous sarcoidosis, hydroxychloroquine appears to be an effective alternative to corticosteroid therapy, although there are no reported randomised controlled trials to support this. An open clinical trial reported 12 out of 17 individuals with regression of cutaneous sarcoidosis within four to 12 weeks of treatment with 2–3 mg/kg daily.[15]

Dermatomyositis

Cutaneous lesions in dermatomyositis often fail to respond to oral corticosteroids. Hydroxychloroquine is reported to be useful for cutaneous involvement,[16] particularly in patients unresponsive to corticosteroids and in those with amyopathic dermatomyositis.[17] Combination antimalarials (with mepacrine) are also reported to be useful.

Lichen planopilaris/frontal fibrosing alopecia

Lichen planopilaris (LPP) is a scarring lymphocytic alopecia, and frontal fibrosing alopecia is a variant of LPP that primarily involves the scalp hair over the frontal hairline and occurs in postmenopausal women. Symptoms and signs of both of these conditions are reported to respond to hydroxychloroquine.[18]

Other conditions

Other skin conditions in which hydroxychloroquine may be used include: disseminated granuloma annulare, chronic ulcerative stomatitis, solar urticaria and Sjogren's syndrome.

Contraindications

The only absolute contraindications are hypersensitivity and a history of retinopathy. Relative contraindications are glucose-6-phosphate dehydrogenase (G6PD) deficiency and neuromuscular disorders, such as myasthenia gravis and psychotic disorders.

Table 2. Adverse effects of hydroxychloroquine

Toxicity	Signs and symptoms	
Ocular	Reversible	Precipitation of the drug in the corneal epithelium in diffuse punctate or whorl-like pattern, which gives rise to visual halos
	Irreversible	Fine pigmentary stippling of the macula Loss of the foveal light reflex 'Bulls-eye' maculopathy Loss of visual acuity Peripheral visual field loss
Haematological	Leucopenia (rare)	
Liver	Transient transaminitis	
Cardiac	Cardiac conduction defects Cardiomyopathy	
Musculoskeletal	Proximal or generalised myopathy	
Skin	Blue-grey pigmentation in patients (10–30%) on long-term treatment Pruritus Morbilliform exfoliative dermatitis Drug reaction with eosinophilia and systemic symptoms Flare of psoriasis	

Pharmacodynamics/pharmacokinetics

Hydroxychloroquine is absorbed in the gastrointestinal tract and it undergoes renal elimination. It is N-demethylated by cytochrome P450 enzymes. Genotype variation in these enzymes could affect efficacy or toxicity. Maximum clinical efficacy can take from three to six months to achieve. Efficacy has been demonstrated, in patients with SLE, to correlate with the drug's blood concentration.[19] A large variability in blood drug concentrations has been reported, with higher concentrations demonstrated in patients with inactive disease, compared with those with active disease, and also a reported association with complete remission of disease.[20,21] Based on these findings, whole blood concentrations in excess of 1,000 ng/ml are recommended. Unfortunately, most NHS laboratories are not able to routinely monitor hydroxychloroquine levels.

Maximum clinical efficacy can take from three to six months to achieve

Mechanisms of action

Potential mechanisms of action have been extensively reviewed, and include intercalation into DNA, phospholipase inhibition, antioxidant activity and inhibition of inflammatory cytokines.[22,23] Hydroxychloroquine accumulates in lysosomes, leading to a rise in pH, which inhibits protease activity, resulting in decreased intracellular processing, glycosylation and secretion of proteins.[24–26] It inhibits stimulation of Toll-like receptors, involved in activation of the innate immune system, which may explain its efficacy

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in the treatment of inflammatory conditions such as LE.[27]

Adverse effects

Ocular toxicity

The incidence of ocular toxicity is reported to be around 50 cases in approximately one million patients treated with hydroxychloroquine (May 2005).[28] In the largest single case series (follow-up after seven years), one case was reported in 1,207 treated patients.[29] In a prospective study of patients treated for more than six years, a total of two out of 400 cases of irreversible hydroxychloroquine retinopathy were observed.[30] The risks of retinal toxicity are much lower with hydroxychloroquine when compared with chloroquine, and these are detailed in Table 2. The British Association of Dermatologists and The British Society for Rheumatology have issued guidelines in conjunction with the Royal College of Ophthalmologists, recommending screening for patients on hydroxychloroquine, including visual assessments at baseline.[28]

Haematological

Antimalarials used in patients with G6PD deficiency are reported to cause haemolysis. Although it is a rare outcome, leucopenia has been reported. Haematological adverse effects are largely reversible after cessation of therapy. Recommendations for monitoring include full blood count at baseline and then monthly for three months, followed by three-monthly tests.

Gastrointestinal side-effects

Gastrointestinal symptoms occur infrequently in patients treated with hydroxychloroquine (10%) and include nausea, vomiting and diarrhoea. Symptoms are usually transient and resolve with time or decreased dosage. Liver function tests should be taken at baseline and then measured monthly for three months, followed by four to six-monthly monitoring.

Cardiac adverse effects

Cardiotoxicity has been reported, in rare instances, and is potentially fatal. Restrictive cardiomyopathy and conduction defects have been reported when hydroxychloroquine is used to treat various rheumatic conditions in which the skin is involved; for example, SLE and scleroderma.[31–33]

Myopathy

Hydroxychloroquine-induced myopathy is uncommon and often difficult to diagnose. It should be considered if there is unexplained evidence of myopathy, such as elevated muscle enzymes (creatine kinase), proximal or generalised muscle weakness, or chest pain. In patients treated for rheumatic diseases, the prevalence is reported to be 12.6% (n=15 out of 119),[34] but can be as high as 46% (n=7 out of 15) in patients treated for cutaneous diseases (LE/granuloma annulare cohort).[35]

Box 1. Monitoring of patients taking hydroxychloroquine (adapted from British Association of Dermatologists/ British Society for Rheumatology guidelines)[28]

- Maximum dose should not be >6.5 mg/kg; total 200–400 mg dose daily
- Check renal and liver function at baseline
- Enquire about visual impairment not corrected by spectacles (at baseline and at annual review)
- Record reading performance with each eye (with glasses if worn) using a near vision test (baseline and annual review)

Monitoring of patients on hydroxychloroquine

Recommendations for monitoring of patients being treated with hydroxychloroquine are summarised in Box 1.[28] In the occurrence of visual impairment, the management options are:

- Referral to optometrist. If the impairment is correctable with refraction, then the patient can commence treatment.
- Referral to ophthalmologist (while on treatment). This can be an onward referral from an optometrist: if there is evidence of reduced vision (especially for reading); if the patient re-

Key points

- Hydroxychloroquine is a well established and widely used treatment in dermatology.
- Side-effects are uncommon, but clinicians should be alert to any new symptoms not explained by the patient's condition.
- Ocular toxicity is much rarer than with chloroquine, but referral to an ophthalmologist is recommended if there are concerns.
- Use of hydroxychloroquine in systemic lupus erythematosus has multiple benefits, including a possible cardioprotective role, but smoking inhibits the therapeutic effect.
- Unexplained chest pain or lethargy in patients taking hydroxychloroquine can be a sign of adverse cardiotoxic effects of the drug.

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ports patchy central vision; or if the patient reports distorted central vision.

- Weaning patient off drug to avoid disease flare.

Conclusion

Hydroxychloroquine is an effective treatment for many cutaneous diseases. Its range of uses among dermatologists continues to broaden. Although side-effects are uncommon, patients must be adequately consented when treatment is commenced. Most adverse effects will resolve on discontinuation of the treatment ■

Declaration of interest
None declared.

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Limitations of systemic therapies for psoriasis

Psoriasis is a common inflammatory and proliferative dermatosis, with a prevalence of 1–3% in most ethnic groups.[1] It is a chronic disease of variable severity and can cause considerable physical and psychosocial morbidity. Its impact on health-related quality of life is comparable to that of other major medical illnesses.[2,3]

A total of 20% of patients with chronic plaque psoriasis require systemic treatment for their disease.[4] Standard systemic therapies include methotrexate, ciclosporin, acitretin and fumaric acid esters. If treatment fails, or is contraindicated, targeted biologic agents can be used.[5]

No treatment is completely curative; suppression of disease or induction of remission are realistic therapeutic goals. The response to any treatment is unpredictable and can be disappointing. Multiple agents may be required for adequate disease control. Contraindications to conventional agents are seen in 9–22% of patients, while adverse events occur in two-thirds.[6,7] The limitations of the individual agents are discussed below.

Methotrexate

Methotrexate is a structural analogue of folic acid. It binds to, and competitively inhibits, the enzyme dihydrofolate reductase, preventing the reduction of folic acid to tetrahydrofolate, an essential step in DNA synthesis, therefore halting cell division in the S phase.[8]

Methotrexate has been used for decades to treat severe psoriasis. Conventional antipsoriatic dosage is low, in the order of 10–25 mg weekly. Low-dose methotrexate has little effect on proliferating epidermal cells *in vitro,* but significantly inhibits proliferating lymphocytes – this probably accounts for its efficacy in psoriasis.[9]

Methotrexate is rapidly absorbed through the gastrointestinal tract, with peak levels achieved within 1.6 hours of ingestion.[10] Excretion is predominantly renal (95%), but there is extensive enterohepatic cycling.[11] Despite a paucity of controlled trials to support its use, the efficacy of methotrexate in psoriasis is definite. Current data suggest that methotrexate produces a reduction in disease severity of at least 50%, in 75% of patients.[12]

The most common symptomatic adverse event is nausea, which occurs in 25% of patients. It is reduced by the co-administration of folic acid.[13] If nausea is intolerable, a divided dose regimen, concurrent anti-emetic therapy or parenteral administration may be considered.

It is well established that chronic methotrexate ingestion can cause hepatic fibrosis. Reported frequencies vary from 14% to 34% and the risk is dose-related.[8] The clinical course of fibrosis is generally slow.[14] Serial liver chemistry test and procollagen III assays should be monitored. If these are persistently elevated, liver biopsy is indicated.[15] If severe fibrosis or cirrhosis is present (Roenigk grade IIIb or IV), treatment should be withdrawn.[16] Hepatotoxicity is increased in the presence of alcohol, so abstinence is advised.[17]

Myelosuppression is the most serious complication of therapy. The rapidly dividing marrow cells are susceptible to the antiproliferative effects of methotrexate, and haematological parameters should be monitored carefully.[18] Two leading causes of acute myelosuppression are renal impairment, which reduces drug excretion, and concomitant administration of antifolate antibiotics.[19] Inadvertent overdose has resulted in several deaths due to acute myelosuppression.[17]

Methotrexate is both abortifacient and teratogenic, and prevention of pregnancy is mandatory.[20] Oligospermia occurs in men; this may persist for some time after treatment and patients should be counselled accordingly.[21]

Ciclosporin

Ciclosporin is a cyclic undecapeptide derived from the soil fungus *Tolypocladium inflatum* Gams. It is a potent immunosuppressant used widely to prevent organ transplant rejection. Its efficacy in psoriasis was first described in 1979.[22]

Ciclosporin is a highly effective, rapidly acting treatment for psoriasis. Robust clinical evidence exists to support its use.[12] It is usually well tolerated, with few symptomatic side-effects. The significant potential for renal toxicity, however, prohibits its long-term use.

Short-term nephrotoxicity is dose-related, due to increased vascular resistance in the renal microcirculation.[23] It is reversible with prompt dose reduction or drug withdrawal.[24] Current guidelines suggest dosage adjustment when the serum creatinine rises from baseline by 30%.[23]

Dose-related hypertension develops in a significant proportion of patients.[25] It should be con-

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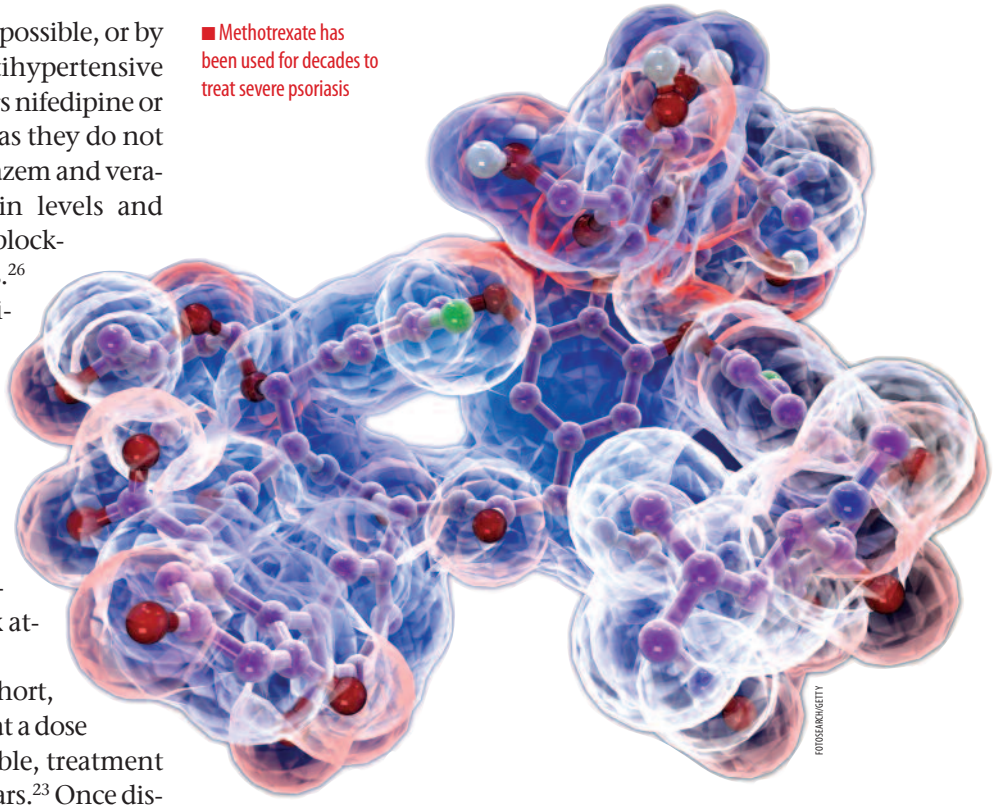
trolled with dose reduction, where possible, or by the addition of an appropriate antihypertensive agent. The calcium channel blockers nifedipine or isradipine are the agents of choice as they do not alter ciclosporin metabolism. Diltiazem and verapamil can alter serum ciclosporin levels and should be avoided, as should beta-blockers and potassium-sparing diuretics.[26]

The risk of malignancy with ciclosporin therapy has caused concern. A prospective five-year study of 1,252 patients treated with ciclosporin for an average of 1.9 years showed a six-fold increase in non-melanoma skin cancer.[27] As this cohort had been exposed to known carcinogens, including psoralen photochemotherapy, the risk attributable to ciclosporin is unclear.

Current guidelines recommend short, intermittent courses of ciclosporin at a dose of 2.5–5 mg/kg daily. Where possible, treatment duration should not exceed two years.[23] Once disease control is achieved, withdrawal of treatment should be planned.



■ Methotrexate has been used for decades to treat severe psoriasis

Acitretin

Acitretin is a second-generation monoaromatic retinoid, and the free acid and active metabolite of etretinate.[28] It replaced etretinate for use in psoriasis in 1993.[11] Acitretin monotherapy is modestly effective in the treatment of chronic plaque psoriasis. At higher treatment doses (approximately 50 mg daily), 50% of patients will achieve a 75% reduction in their Psoriasis Area and Severity Index score (PASI 75 response).[29] Clinical response is generally slow, beginning at three to four weeks and peaking at three to six months.[30]

The undoubted teratogenicity of retinoids precludes their use during pregnancy.[31] Although acitretin is less lipophilic than etretinate, an unpredictable reverse-esterification to etretinate occurs in the presence of ethanol.[32] Prevention of pregnancy is mandatory during, and for two years after, treatment with acitretin.[33] Therefore, it is usually not used in women of childbearing age.

Mucocutaneous adverse events are common and dose-related; cheilitis occurs in 94% of patients receiving 50–75 mg of acitretin per day.[34] The reported risk of telogen effluvium varies from 10% to 75% and can cause significant patient distress. It is dose-related and reversible, but, on occasion, necessitates withdrawal of treatment.[30]

Hypertriglyceridaemia occurs in 66% of patients, while elevation in total cholesterol levels occurs in one-third.[35] Regular monitoring of lipid levels is essential throughout treatment. Lipid abnormalities can be managed by reducing the dose of acitretin, diet and lifestyle modification or by the use of lipid-lowering agents.

Transient elevations in transaminases have been reported in one-third of patients taking acitretin for psoriasis. However, no evidence of hepatotoxicity was discovered in a prospective two-year study of pre- and post-treatment liver biopsies.[36] Severe hepatotoxic reactions have occurred but these are considered idiosyncratic and rare.[37]

Fumaric acid testers

Fumaric acid is a naturally occurring organic acid.[38] Self-experimentation by the German chemist Schweckendiek led to the discovery that fumaric acid esters were useful in the treatment of psoriasis.[39] The commercially available preparation, Fumaderm® (Almirall Hermal), contains dimethylfumarate and the calcium, magnesium and zinc salts of monoethylfumaric acid.[40] It is licensed in Germany for the treatment of severe, relapsing psoriasis vulgaris, which is refractory to conventional therapy.[38] Unfortunately, it is not licensed in the UK and is only available on a named-patient basis. A dose-escalation protocol is employed, starting with 30 mg daily, increasing to a maximum dosage of 240 mg three times daily.[41]

Fumaric acid esters are effective, if tolerated. Controlled clinical trials have shown a 50–80% reduction in PASI score after 16 weeks of therapy.[12,42] Unfortunately, symptomatic side-effects are common, resulting in treatment withdrawal in approximately 10% of patients.[12] Gastrointestinal side-effects occur most commonly (two-thirds of

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patients) and are maximal between Weeks 4 and 12 of treatment. They are dose-related and typically self-limiting. Flushing occurs in one-third and can cause significant discomfort.[11]

Asymptomatic adverse events are also important. Lymphopenia is almost universal (94% of patients) and necessitates regular monitoring of full blood count. A lymphocyte count below 0.5 x 10^9/l is an indication for dosage reduction.[38]

Early case reports of acute renal failure associated with fumaric acid therapy have not been supported by controlled clinical trials, which showed no evidence of nephrotoxicity.[42,43,44] Nonetheless, renal function should be monitored throughout treatment.[39]

Biologic therapy

Biologic molecules are proteins, created using recombinant DNA techniques, designed to interact with existing human proteins or their cellular receptors.[45] Increased understanding of the immunopathogenesis of psoriasis has led to targeted biologic therapies for this disease. These 'biologics' modulate key pathogenic steps in the psoriatic immunological cascade. Two classes of these drugs are currently licensed for use in psoriasis: the tumour necrosis factor (TNF) inhibitors infliximab, adalimumab and etanercept, and the interleukin-12/23 (IL-12/23) antagonist ustekinumab.

TNF inhibitors

TNF-alfa (TNF-α) is a key pro-inflammatory cytokine in psoriasis.[46] It is up-regulated in lesional versus non-lesional skin, and both skin and serum levels correlate with severity of the disease.[47]

The TNF inhibitors currently licensed for use in psoriasis include infliximab, adalimumab and etanercept. Infliximab and adalimumab are monoclonal antibodies to TNF-α and etanercept is a soluble receptor. Large randomised trials have demonstrated clear efficacy in psoriasis, with 50–80% of patients achieving a PASI 75 response.[48]

Similar to other biologic agents, the TNF inhibitors lack traditional end-organ toxicity. They have fewer contraindications than oral systemic agents and require less frequent monitoring of laboratory parameters.[49]

Important concerns exist regarding the safety of TNF inhibitors. The long-term adverse event profile has not been elucidated. As potent immunosuppressants, infection and malignancy risks are of primary concern. Registries such as the British Association of Dermatologists Biologics Interventions Register have been established to assess the long-term efficacy and safety of these therapies.[50]

TNF inhibitors confer an increased risk of developing clinically active tuberculosis. This risk has not been exactly quantified, but may be fivefold.[51] A preponderance of tuberculosis early in treatment suggests reactivation of latent tuberculosis.[52] Screening for latent tuberculosis is, therefore, mandatory prior to initiating anti-TNF therapy.[51,52]

TNF-α promotes a cytotoxic T-cell response to B-cell malignancies.[53] It is, therefore, biologically plausible that TNF inhibitors might increase lymphoma risk. The issue is complicated by the increased risk of lymphoma conferred by several autoimmune diseases, including psoriasis. The reported relative risk of developing lymphoma following anti-TNF therapy varies from 0.8 to 4.9.[54] In view of such discrepant data, close surveillance of patients is warranted.

Although TNF blockade should, theoretically, improve cardiac dysfunction, the converse has repeatedly been demonstrated.[55,56] Current guidelines, therefore, recommend that TNF inhibitors be avoided in patients with New York Heart Association Class III or IV congestive cardiac failure and used with caution in heart failure of lesser degrees.[57]

As well as assessing the efficacy and safety of biologic agents in psoriasis, registries have assessed drug survival. Drug survival measures the length of time that a patient is treated with a certain therapy. The main reason for a lack of drug survival in a patient is loss of efficacy or the development of intolerable side-effects. This may be, in part, due to the development of neutralising antibodies. Some studies have reported that infliximab has the best drug survival of the biologics.[58] This study reported a 70% four-year drug survival with infliximab compared with 40% for etanercept and adalimumab. A second study, in contrast, reported a much shorter drug survival with infliximab compared with etanercept and adalimumab.[59] The number of studies on drug survival is limited to date, but the data from future registry reports should clarify drug survival for biologics.

IL-12/23 antagonists

Under the influence of IL-12 or IL-23, CD4+ T-cells can develop into T helper-1 (Th1) or T helper-17 (Th17) cells, respectively.[60] Both Th cell subtypes play a crucial role in the immunopathogenesis of psoriasis.

Ustekinumab is a fully human monoclonal antibody, which binds to the shared p40 protein subunit of human IL-12 and IL-23 with high affinity and specificity, preventing interaction with their cell surface IL-12Rβ1 receptor.[60] By inhibiting the activity of IL-12 and IL-23, ustekinumab suppresses the formation of Th1 and Th17 cells.[60] It is administered by subcutaneous injection (either 45 or 90 mg) at zero and four weeks initially, and every 12 weeks thereafter.

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QV™ Feel the difference

As the year turns around and the lambs gambol in the fields once more, the machine that is the Primary Care Dermatology Society (PCDS) gears up for another year of education. In recent years, our portfolio has expanded far beyond the confines of our seasonal, regional meetings to include a much broader range of dermatological disciplines.

Our successful Essential Dermatology (ED) courses now enter their third year, and the juggernaut rumbles on to pastures new. This has become a roadshow that takes the PCDS to all corners of this fair country – this year from Warrington to Colchester. In addition to this, we now have a Level 2 course, which adds another layer of dermatological delights to the primer course. In recent years, we have encouraged the masses to learn the dark art of dermoscopy and, once again, we have several courses aimed at both the beginner and the more experienced practitioner.

We hope that you are inspired to come along to one of our meetings, and leave it even more inspired! Our next general courses will be in London in June and Nottingham in September, and the annual extravaganza that is the Scottish meeting is in November. The ED, ED Level 2 and dermoscopy courses are too many to mention here – see below!

The PCDS is, however, more than just a provider of courses. We work behind the scenes, in a number of theatres, carrying the burning brand of primary care dermatology on behalf of both our members and the wider primary care community. We represent our members at the Department of Health, Parliament, the British Association for Dermatologists, the Dermatology Council for England/Scotland, and in many other committee/meeting rooms too.

We also have spent the last couple of years building a website (and never miss an opportunity to say so) that, we hope, bears comparison to any site out there. It is continuously being updated by our webmaster (although I prefer to think, as do 'QI', of it as being done by the PCDS elves) and I commend its contents to the house. There are tutorials, educational resources, an image library, a dermatology primer and links to other useful sites. It is also the source of all relevant information regarding the courses mentioned above. We hope to be able to welcome you to at least one event! Come along and see what we have to offer – we don't bite, you may even enjoy yourself.

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The safety and efficacy of ustekinumab in psoriasis was assessed in two large, Phase III, multicentre clinical trials involving almost 2,000 patients (PHOENIX 1 and PHOENIX 2).[61,62] A total of 66% and 76% of patients receiving the higher dose of 90 mg achieved a PASI 75 at 12 weeks, compared with 3% and 4% of patients receiving placebo.

Subcutaneous ustekinumab appears to be well tolerated with a favourable adverse event profile. Common adverse events reported in both trials included upper respiratory tract infections (2.9–7.1% of ustekinumab recipients versus 6.3% and 3.4% of placebo recipients), nasopharyngitis (6.8–10.2% versus 8.6% and 7.1%), arthralgia (2.4–3.4% versus 2.7% and 2.9%), and headache (4.6–5.5% versus 2.4% and 4.1%).

Serious adverse events were uncommon, occurring in ≤2% of patients (0.8–2% of ustekinumab recipients versus 0.8% and 2% of patients receiving placebo).[63] There was no significant increase in the incidence of infections (21.5–31.4% in ustekinumab recipients versus 26.7% and 20.0% of patients receiving placebo), serious infections (0.0–0.8% versus 0.4% and 0.5%), cutaneous malignancy (0.0–0.2% versus 0.0% and 0.2%), non-cutaneous malignancy (0.0% versus 0.0% and 0.2%) or cardiovascular events (0.0–0.4% versus 0.0%).

No mycobacterial infections occurred in up to 76 weeks of continuous ustekinumab therapy. Although this is reassuring, caution is warranted; severe mycobacterial infections have been reported in individuals congenitally deficient in IL-12 p40 and the IL-12Rβ1 receptor.[64] Pre-treatment screening for latent tuberculosis is, therefore, also mandatory in this group. Long-term studies have confirmed the findings of both good efficacy and safety of ustekinumab in earlier studies.[65]

Another monoclonal antibody to IL-12/IL-23 (briakinumab) has been withdrawn from further development. This withdrawal primarily concerned the development of an excess number of major adverse cardiovascular events in patients treated with briakinumab compared with placebo.[66] A meta-analysis of cardiovascular events in patients treated with IL-12/23 inhibitors (briakinumab and ustekinumab) reported a non-significant increase in cardiovascular events in treated patients compared with placebo.[67]

Summary

The management of moderate-to-severe psoriasis is challenging. There are limitations with all established systemic agents, but the majority of patients tolerate them and have successful outcomes. Biologic therapies offer exciting alterna-

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tives, but with the relative absence of long-term safety data, caution should be exercised ■

Declaration of interest
None declared.

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Key points

- **Approximately 20% of chronic plaque psoriasis patients require systemic treatment. Psoriasis can be suppressed, or go into remission, but the disease cannot be completely cured.**
- **While most patients have successful treatment with established systemic therapies, these are all associated with some degree of side-effects.**
- **Fumaric acid esters are an effective psoriasis treatment but, again, symptomatic side-effects are common.**
- **Biologic agents are an exciting alternative to systemic agents; they are an effective treatment with fewer side-effects. However, more research needs to be done into their long-term effects.**

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DERMATOLOGY IN PRACTICE 2013; Vol 19 No 1

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Sofa dermatitis – the rise and fall of an allergen

An outbreak of contact dermatitis can be exciting and challenging to investigate. Occasionally, a series of cases involving sensitisation to a particular allergen emerges. One such outbreak occurred in 2006. This short article sets out the story of how the problem arose, and how, with good communication and international collaboration between centres investigating contact dermatitis, the cause was identified and the problem largely eliminated.

Background

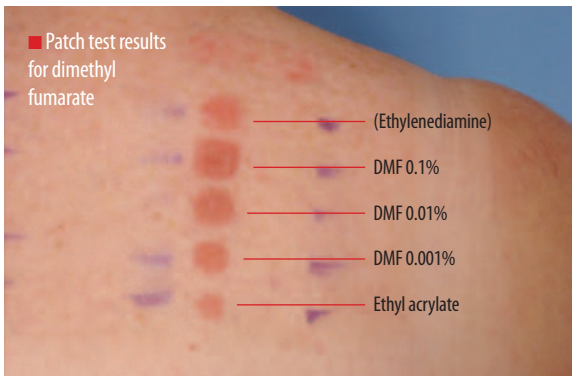
In the autumn of 2006, cases of severe dermatitis, mainly affecting patients' posterior thighs, buttocks and backs, started to present to dermatologists in the UK and Finland,[1–3] and there were subsequent reports from France of similar cases. The rash was eczematous and, in some cases, so florid that hospitalisation was required. Some patients, who were already known to have psoriasis, went on to develop severely eczematised psoriasis.

The pattern of the dermatitis, which was sometimes interestingly distributed, was suggestive of contact dermatitis. Some patients described symptoms of airborne allergen exposure. Several reported that the condition was alleviated when they went on holiday, but recurred on returning home. In addition, the patients reported that the onset of their dermatitis seemed to arise a short time after they had taken delivery of new leather furniture. Therefore, it was suspected that contact with leather furniture was the probable cause. However, the contact was not direct, as most of the patients only sat on the furniture when fully clothed. Covering the furniture with a rug or 'throw' had no positive effect on the condition. Treatment with potent topical corticosteroids showed little results, and many patients required systemic steroids.

Investigation

It soon became clear that the rash was indeed connected to leather furniture purchased from a variety of popular stores that shared the same manufacturer in Southern China. Several investigators requested information from this manufacturer, but it seemed that there was great reluctance to disclose full details about the chemicals that were used in the manufacturing process.[1] Therefore, dermatologists in the UK and Finland worked hard to identify what might be causing the problem, as routine patch testing had not uncovered the responsible allergen. It was not clear whether the leather furniture had been contaminated by an unknown substance, or whether the leather fabric itself was the source of the outbreak, as patch testing to samples of the leather fabric proved to be inconclusive. Investigators then collaborated with experts in chemical analysis, which proved to be rewarding.[4]

Eczema of the right thigh



Patch test results for dimethyl fumarate

An investigation in the UK involved taking samples from the suspected furniture and testing the various parts.[5] Initial testing proved negative, but it was then discovered that deep inside the furniture were some sachets, which were found to contain a fungicidal agent used to prevent mould growth on the leather. It had been introduced for this purpose in 2005, but was not declared by the

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manufacturers. The investigators in the UK and Finland collaborated with Swedish experts in chemical analysis. Thin layer chromatograms (TLC) were prepared for skin testing with separated chemicals extracted from the material.[4] Dimethyl fumarate (DMF) was identified from the skin-test positive spot of the TLC strips prepared from the textile extracts of the furniture. The patients with a furniture-related dermatitis had positive patch test reactions to DMF. The mysterious substance in the sachets found within the furniture was then tested, and identified as DMF.

The irritating and sensitising properties of DMF were reported by de Haan *et al.*[6] DMF is a substance that sublimates (changes on heating from a solid to gaseous state without going through a liquid state). On the basis of these investigations, a patch test series for the furniture-related dermatitis patients was developed. It was suspected that concurrent reactions to methacrylates might be identified because of cross-reactivity.

Patients were patch tested to serial dilutions of DMF and, additionally, in some centres, to dimethyl maleate, methyl acrylate, ethyl acrylate and methyl methacrylate.[7] Those with sofa dermatitis demonstrated positive patch test reactions to DMF and some showed positive cross-reactions to the other chemicals tested. This sensitivity to the related chemicals would increase their risk of future problems if exposed to these substances in, for example, an occupational setting.

Public response

The retailers of the leather furniture in question received thousands of complaints from the patients affected by this epidemic. This was fuelled by the press – in particular, the national television programme 'Watchdog', which originally highlighted the problem. In response to the complaints, some of the retailers accepted liability and offered either a refund or replacement furniture. However, some patients found that the retailers refused to accept responsibility for the skin complaints and instructed solicitors to proceed with personal injury claims on their behalf. Some of the solicitors promoted the potential for customers who had subsequently developed a skin rash to claim for compensation in the press. The dermatitis resolved when the leather furniture was removed from the vicinity of the patient.

Further to this, dermatologists in Spain started to see another outbreak of contact dermatitis, this time caused by shoes made in China.[8–10] These were mainly caused by boxes where anti-mould sachets were present, but this was not always the case; some shoes were sold unboxed, without the sachets. The results of the investigations showed that the source of this problem was also DMF. In many instances the shoes were still contaminated, despite having been out of the box for a prolonged period. For this reason, patients presenting with dermatitis of the feet should be patch tested to a series that contains DMF. In addition to footwear, there have also been reports of DMF contaminating clothing, including jeans, riding helmets and work uniforms.[11] Therefore, DMF tests should be added to a textile battery of patch tests.

Since 2009, the European Commission has prohibited any trade of products containing a DMF concentration higher than 0.1 mg/kg.[12] This directive applies to new products entering the market. It does not, however, apply to second-hand items and, therefore, it is important to be vigilant and report new cases that have a similar presentation.

Conclusion

These cases demonstrate how collaboration between clinicians and scientists, both at home and abroad, can solve a mysterious condition and help the public by alerting them to potential risks. Invoking new European legislation has lessened these risks, but has not eliminated the problem ■

Declaration of interest
None declared.

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Key points

- A vital contributing factor to the discovery of the exact source of the allergic reactions was the collaboration between clinicians and experts in chemical analysis.
- The responsible allergen, dimethyl fumarate (DMF), has also been reported as being present in shoes, clothing and riding helmets.
- Since 2009, the European Commission has prohibited the trading of products with a concentration of DMF higher than 0.1 mg/kg.

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DERMATOLOGY IN PRACTICE 2013; Vol 19 No 1

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Going like a bomb

On my first day as a clinical medical student, more years ago than I care to remember, I attended a lecture given by a distinguished psychiatrist. He explained to us that our career choices as doctors were psychologically predetermined. Orthopaedic surgeons, for example, were little boys who did not wish to grow up and who wanted to spend their lives playing with Meccano®. General surgeons, he explained, had psychopathic personalities, apparently ready to rip open people's abdomens and pull out their entrails at the drop of a hat. He went through each specialty explaining the particular characteristics of the doctors who chose that as their career and, as he did so, each of them appeared as unappealing as the next. Finally, as he reached the end of his lecture, and was just stepping off the stage, he said, 'Oh I nearly forgot dermatologists, they are all sexual perverts'.

Different medical specialties attract very different personality types

I was a very naive 21-year-old at the time who had no idea at all what a sexual pervert was and could not wait for the dermatology attachment to find out. When dermatology eventually came around in my final year, I was left none the wiser and after over 30 years in the specialty, I am still somewhat baffled by his strange assertion. I can only imagine that he had had some unhappy experience in his formative years.

Nevertheless, I am sure that his basic idea that different medical specialties attract very different personality types is undoubtedly true. So, what would he have made of the new phenomenon within the NHS of doctors who abandon a clinical career to become medical managers. Personally, I am not sure that medicine has been well served by some of those who have followed this particular career path. In my experience, all too many of them have chosen this as a career move to escape from their frustrations with clinical practice, whereas what has really been needed are the very best and able clinicians, who are capable of inspiring the rest of us.

A few years ago, there was a fascinating programme on television about how the Army trains those extraordinary and selfless men and women who become bomb disposal officers. The selection process involves very detailed psychological profiling and, as one of the officers in charge of this explained, anyone who actually volunteered was automatically rejected as being entirely unsuitable. It sometimes occurs to me that the same criterion might be usefully applied to other occupations and, from my own observations, the NHS might well have benefited if this rule had been applied in the selection of medical managers as well.

Thankfully, there is no truth in the generalisation that general surgeons harbour psychopathic tendencies

DIGITAL VISION/GETTY

Declaration of interest
None declared.

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DERMATOLOGY IN PRACTICE 2013; Vol 19 No 1

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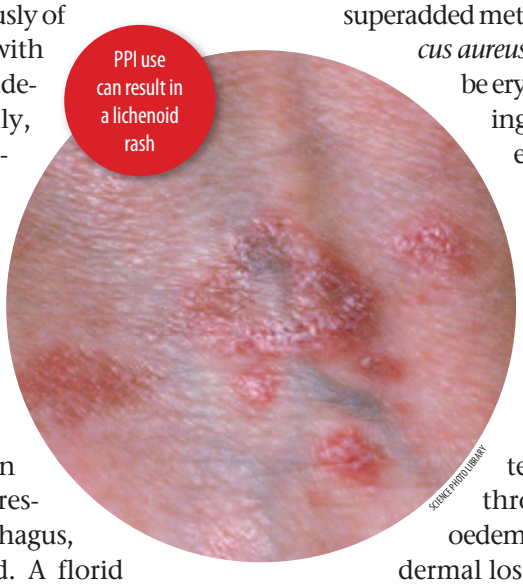
Fatal lichenoid drug eruption after proton pump inhibitor therapy

This case discusses a patient who developed a severe lichenoid drug eruption following treatment with the proton pump inhibitors (PPIs) lansoprazole, omeprazole and esomeprazole.

A 78-year-old lady, previously of good health, was admitted with a four-month history of a widespread pruritic rash. Initially, she had been started on lansoprazole for dyspepsia, but developed a rash several days later. Lansoprazole was discontinued and the patient was switched to omeprazole. The rash recurred and the offending drug was, again, stopped. Two months later, when an endoscopy revealed the presence of likely Barrett's oesophagus, esomeprazole was initiated. A florid rash developed within two weeks, resulting in admission. At that time the drug was stopped.



PPI use can result in a lichenoid rash

Further examination

Examination revealed a widespread, non-blanching vasculitic-type eruption, with areas of annular scaly erythema affecting the face, scalp, torso and limbs. There were no areas of epidermal detachment or mucosal involvement. Skin biopsy confirmed changes consistent with a lichenoid drug reaction, in addition to vasculitic features. Autoantibody screening was negative.

The patient responded well to topical treatment and was subsequently discharged. Unfortunately, when she attended for follow-up some weeks later the rash had become confluent. She was erythrodermic, short of breath, had lost weight and had developed widespread lymphadenopathy. At this point, she was readmitted for further investigations.

Repeat skin biopsy showed similar features as before. T-cell receptor gene analysis excluded cutaneous lymphoma. CT scanning revealed multiple pulmonary emboli and inguinal lymphadenopathy. Lymph node biopsy confirmed dermatopathic nodes. The patient was discharged and given an urgent clinic review appointment as her skin responded to topical treatment.

She was then readmitted less than a week later due to wound dehiscence at the biopsy site with superadded methicillin-resistant *Staphylococcus aureus* infection. She continued to be erythrodermic, and was increasingly oedematous with dependent bullae formation. Her nutritional status was poor and her albumin levels had fallen to 14 g/l.

She was treated aggressively on the ward with intravenous antibiotics and nasogastric feeding, but her condition continued to deteriorate. She remained erythrodermic with extensive oedema and areas of superficial epidermal loss. A short stay in a high-dependency unit followed after contracting hospital-acquired pneumonia. She developed bilateral pleural effusions that required drainage. The effusions recurred causing subsequent cardiac failure, resulting in her death.

Discussion

This lady developed a lichenoid drug eruption following treatment with three different PPIs. Each time a PPI was introduced, the rash recurred; skin biopsy confirmed a drug reaction.

The classic complications of erythroderma can be found in this case; sepsis, hypoalbuminaemia and cardiac failure – all of which contributed to this patient's final demise.

To the best of our knowledge, there have been no studies looking at the cross-reactivity of PPIs. One may expect that a 'class effect' exists due to their similarly substituted benzimidazole structure. We advocate that, until further data are available, caution is required in prescribing sequential PPIs following a documented drug rash with one agent, as class effect may have a significant role to play ■

Declaration of interest.
Both authors declare that there is no conflict of interest.

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New technologies to aid in the diagnosis of malignant melanoma

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In primary care, it is becoming increasingly important to be able to recognise malignant melanoma at an early stage. The earlier it is diagnosed, the better the prognosis. In 2008, there were 11,767 new diagnoses of melanoma in the UK, and its prevalence currently stands at one in 61 males and one in 60 females. In the same year there were 2,070 deaths due to melanoma.[1] The National Institute for Health and Clinical Excellence (NICE) recommends that any pigmented lesion, which cannot be diagnosed with certainty as benign, should be referred under the two-week wait protocol to an expert for urgent assessment. Sorting the innocent from the suspicious can be tricky, especially for GPs faced with a deluge of pigmented lesions to assess, often in a seasonal way. In this article, we review the literature regarding currently available tools, or those on the horizon, that might help with diagnosing potentially malignant skin lesions.

Current algorithms and checklists

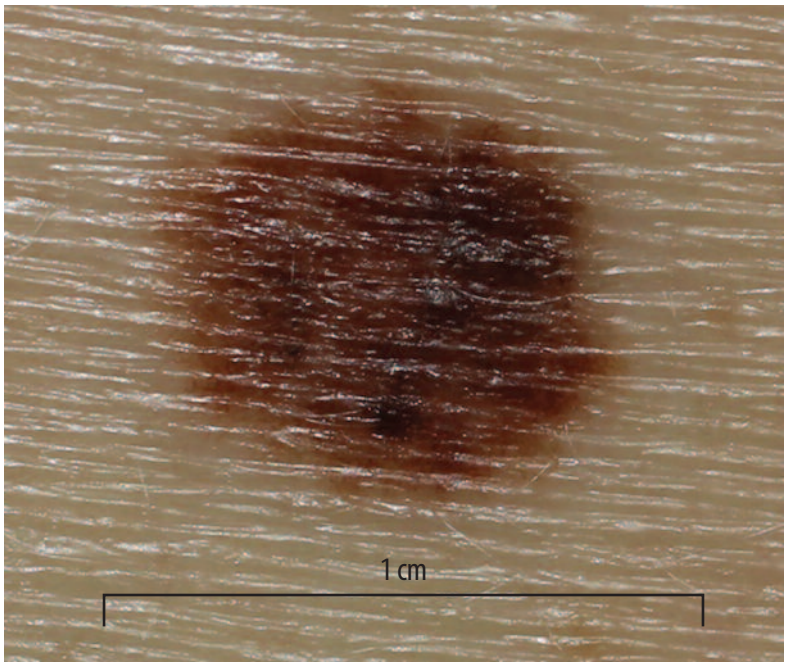
The seven-point checklist is the current norm in the primary care field. This was developed in the 1980s to help non-dermatologists (doctors and patients alike) detect features of a naevus that may be indicative of melanoma. As of 2005, its modified form (see Table 1)[2] has been recommended by NICE for use in general practice, to help identify suspicious skin lesions and potential melanomas that may require referral. Any one feature can be suspicious enough for referral, but a score of 3 or more offers a strong case for referral.[2] Figure 1 shows a clinical photograph of a pigmented lesion on the back of a 40-year-old lady with a with a history of a previous melanoma. The patient was unaware of any change. The dermatologist providing follow-up recognised that the lesion was new, appeared to have some blue/black colouration in it and was, approximately, 8 mm in diameter. On the seven-point check-list it would score 2 each for change in size and colour as well as 1 for being greater than 7 mm diameter.

A recent systematic review by Whited and Grichnik concluded that the seven-point checklist was a useful tool, having a high sensitivity that ranged from 79% (95% confidence interval [CI]: 70–85) for an unreported specificity to 100% (95% CI: 94–100) for a specificity of 37% (95% CI: 28–46). The seven-point checklist had a low specificity, which resulted in a number of benign lesions being classified as malignant. They felt that 'better study designs are necessary to define the operating characteristics of physicians' examination for detecting the presence or absence of melanoma'.[3] It should be noted that all the studies reviewed were on patients who were pre-screened and referred to secondary care. To date, there has not been a published paper validating the seven-point checklist in the primary care setting.

Table 1. The seven-point checklist

	Clinical features	Score
Major features	• Change in size • Irregular shape • Irregular colour	2 for each
Minor features	• Largest diameter 7 mm or more • Inflammation • Oozing • Change in sensation	1 for each

A score of 3 or more is regarded as suspicious



■ **Figure 1.** Clinical photograph of a pigmented lesion

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Dermatoscopy – the gold standard?

For many years, dermatologists have been using dermatoscopes to aid in the diagnosis of potentially malignant skin lesions. The principle is that of a bright magnifying search light, which can look through the *stratum corneum* by rendering it transparent, either by using a liquid interface such as oil or alcohol (non-polarising dermatoscopes) or by using a polarised light filter (thus not requiring direct contact). Either approach gets light into, and out of, the skin to a deeper level so that the observer can see light that has been backscattered by the deeper structures in the skin and, thus, interpret its morphology.

A systematic review of the literature by Kittler *et al* showed that the use of dermatoscopy could improve the diagnosis of melanoma, compared with inspection by the unaided eye. Most of the dermatoscopy literature comes from secondary care and emphasises that this approach should not be recommended for untrained users.[4] A further systematic review, by Rajpara *et al,* has demonstrated that there were no significant differences in the diagnostic performance of various dermatoscopy algorithms, whether looking for features or patterns. They derived a pooled sensitivity of 88% and specificity of 86% for a diagnosis of melanoma. However, these results need to be confirmed by a large-scale, high-quality, population-based study.[5]

To test if dermatoscopy can be more accessible to primary care practitioners, a simplified three-point checklist has been advocated (see Table 2).[6]

A subsequent internet-based study followed the learning of 150 participants who underwent a web-based tutorial, comprising a training set of images followed by a test set of 150 lesions. The overall sensitivity for a diagnosis of melanoma was 94% (95% CI: 89.4–96.6%) and specificity was 71.9% (95% CI: 58.1–82.5%). It is important to note that the images came from excised specimens from a specialist centre for pigmented lesions, with 49 of the 150 lesions being malignant (basal cell carcinomas or melanomas), thus not representing the real world of primary care. The kappa statistic for interobserver agreement was only 0.53 in experienced observers, and 0.45 in non-experienced observers. The specific features of an atypical network (usually found in early melanoma) and blue-white structures (found in both melanoma and pigmented basal cell carcinoma) are harder for the novice to recognise, but partcipants demonstrated improvement in learning how to do this, as a result of the tutorial system.[7]

Use of dermatoscopy could improve the diagnosis of melanoma

Reported improvements in the sensitivity for melanoma, in the few studies undertaken on dermatoscopy in general practice, have not carried with them an improvement in specificity, or reduction in referral or biopsy of benign lesions. Menzies *et al* have evaluated the effects of adding not just dermatoscopy to the naked eye examination in primary care, but also short-term sequential imaging. They were able to show an increased confidence in the diagnosis of benign lesions, thereby reducing referral. Crucially, the short-term imaging review eventually identified one-third of the detected melanomas (with a maximum Breslow depth of 0.65 mm). Thus, close follow-up at three months (where there is uncertainty about a pigmented lesion) with high-quality carefully-archived dermatoscopic images is a valid strategy – with the literature supporting it is a safe approach. The downside is that the online education in this study took ten to 20 hours for most GPs, so only 62% of those initially recruited to the study completed the training. The image acquisition tool (SolarScan® Sentry [Polartechnics Ltd]) is a high-resolution digital dermatoscope.[8]

The ubiquity of mobile telephones with cameras has led to the development of attachments to take dermatoscopic images (for example, FotoFinder's handyscope® [see Figure 2]). There is the possibility that these devices, if arranged in a structured, secure and protocol-driven way, could form the basis of ongoing studies in the primary care setting, testing the value of the seven-point checklist, the dermatoscopy three-point checklist and short-term sequential dermatoscopy imaging

Table 2. The dermatoscopy three-point checklist

Asymmetry	Asymmetrical distribution of colours and dermatoscopic structures
Atypical network	Pigmented network with irregular holes and thick lines
Blue-white structures	Any type of blue and/or white colour

The presence of more than one criterion suggests a suspicious lesion

Figure 2. FotoFinder's handyscope® attachment for the iPhone

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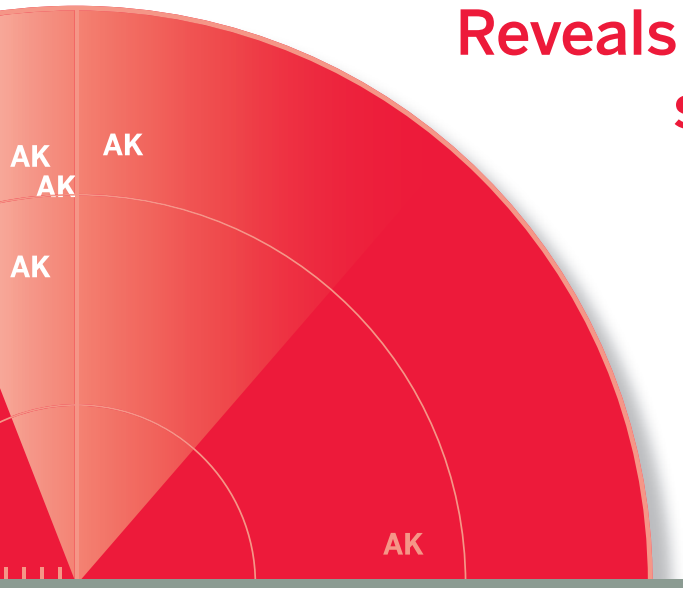

Zyclara 3.75% cream (imiquimod). Indications: Zyclara is indicated for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic, visible or palpable actinic keratosis (AK) of the full face or balding scalp in immunocompetent adults when other topical treatment options are contraindicated or less appropriate. **Dosage:** Treatment should be initiated and monitored by a physician. Apply up to 2 sachets, once daily, before bedtime to the skin of the affected treatment area for two treatment cycles of 2 weeks each separated by a 2-week no-treatment cycle or as directed by the physician. The treatment area is the full face or balding scalp. The safety and efficacy of imiquimod in AK in children and adolescents below the age of 18 years have not been established. For external use only. Contact with eyes, lips, and nostrils should be avoided. The treatment area should not be bandaged or otherwise occluded. Apply as a thin film to the entire treatment area and rub in until the cream vanishes. Partially-used sachets should be discarded and not reused. Leave on the skin for approximately 8 hours; after this time it is essential that the cream is removed by washing the area and the hands with mild soap and water. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and precautions:** Lesions clinically atypical for AK or suspicious for malignancy should be biopsied to determine appropriate treatment. Not recommended until the skin has healed after any previous medicinal products or surgical treatment. Use of sunscreen is encouraged, and patients should minimise or avoid exposure to natural or artificial sunlight. Not recommended for the treatment of AK lesions with marked hyperkeratosis or hypertrophy as seen in cutaneous horns. During therapy and until healed, affected skin is likely to appear noticeably different from normal skin. Local skin reactions are common but generally decrease in intensity during therapy or resolve after cessation of therapy. Rarely, intense local inflammatory reactions including skin weeping or erosion can occur after only a few applications. There is an association between the complete clearance rate and the intensity of local skin reactions. These local skin reactions may be related to the stimulation of local immune response. Imiquimod has the potential to exacerbate inflammatory conditions of the skin. If required by the patient's discomfort or the intensity of the local skin reaction, a rest period of several days may be taken. Treatment can be resumed after the skin reaction has moderated. The intensity of the local skin reactions tend to be lower in the second cycle than in the first treatment cycle. Flu-like systemic signs and symptoms may accompany, or even precede, intense local skin reactions and may include fatigue, nausea, fever, myalgias, arthralgias, and chills. An interruption of dosing or dose adjustment should be considered. Use with caution in patients with reduced haematologic reserve. Patients with cardiac, hepatic or renal impairment were not included in clinical trials. Caution should be exercised in these patients. Use with caution in immunocompromised patients and/or patients with autoimmune conditions and consider balancing the benefit of treatment for these patients with the risk associated either with the possibility of organ rejection or graft-versus-host disease or a possible worsening of their autoimmune condition. No data are available on re-treating AK that have cleared after two cycles of treatment and subsequently recur. Stearyl alcohol and cetyl alcohol may cause local skin reactions. Methyl parahydroxybenzoate (E 218), and propyl parahydroxybenzoate (E 216) may cause allergic reactions (possibly delayed). No interaction studies have been performed but use with caution in patients who are receiving immunosuppressive drugs. Avoid using with any other imiquimod creams in the same treatment area. No data are available on the use of Zyclara during pregnancy or breast-feeding and there are no data on the risk to human fertility. There is no or negligible influence on the ability to drive or use machinery. **Side effects:** Herpes simplex, skin infection, lymphadenopathy, haemoglobin, white blood cell and platelet counts decreased, anorexia, blood glucose increased, insomnia, depression, headache, dizziness, nausea, diarrhoea, vomiting, erythema, scab, skin exfoliation, skin oedema, skin ulcer, skin hypopigmentation, dermatitis, erythema multiforme, Stevens Johnson syndrome, cutaneous lupus erythematosus, skin hyperpigmentation, myalgia, arthralgia, application site effects, including erythema, scabbing, exfoliation, dryness, oedema, ulcer, discharge, reaction, pruritus, swelling, burning, irritation and rash, fatigue, pyrexia, influenza like illness, pain, chest pain. Consult the Summary of Product Characteristics before prescribing, particularly in relation to side effects, precautions and contraindications. **Legal Category:** POM. **Package quantity and basic NHS price:** Pack of 28 sachets £113.00. **Product licence number:** EU/1/12/783/002. **Marketing authorisation holder:** Meda AB, Pipers väg 2A, 170 73 Solna, Sweden. **Date of preparation of prescribing information:** January 2013. UK/ZYC/13/0003

Adverse events should be reported.
Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Meda Pharmaceuticals Ltd.

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UK/ZYC/13/0005 Date of preparation: February 2013.

MEDA

for the recognition of suspicious pigmented lesions and triaging of benign lesions.

Smartphone and tablet software

There are a number of smartphone apps that claim they can be useful in the detection of malignant melanoma, using simple algorithms and shape analysis features. However, only one study of any note has been published to date. Skin Scan® is an app for iPhone® with a dermatoscopic attachment. The app combines image processing with the seven-point checklist. Wadhawan *et al* reported a sensitivity of 87.27%, and a specificity of 71.31% (CIs not specified). This study was limited by the fact that only lesions they classified to be 'low difficulty' were used.[9]

Figure 3. MoleMax® is a polarised light dermatoscope combined with software

IMAGE REPRODUCED WITH PERMISSION FROM DERMA MEDICAL SYSTEMS

Assisting computer software

Thus far, the emphasis has been on training the non-expert to recognise features or patterns, derived by experts, as key determinants of whether a lesion is suspicious or not. There have been, and continue to be, many approaches to try and either present information to the non-expert, to make the diagnosis more certain, or to artificially process the image information to derive a diagnosis, or a probability of 'suspicious' for melanoma. Studies are mostly centred in secondary care, but their outputs are beginning to spill over into primary care settings, with or without validation.

MoleMax®(Derma Medical Systems), in its various forms, is a polarised light dermatoscope, combined with software that offers a step-by-step walk through the seven-point checklist using multiple choice questions (see Figure 3). When combined with the DermaNet server, any image that the clinician feels may be suspicious can be sent through, and within two days the company will send back three histopathologically similar lesions, with a diagnosis for each of them from their library. This may enable a clinician to make a more informed diagnosis of a suspicious legion. MoleMax's automated Mole Score software offers a computer-based calculation of the risk using their library and the 'ABCD rules'. We have not been able to locate a study on its use to date.

SolarScan works on non-polarised light dermatoscopy and a semi-automated analysis system. Multiple features are analysed against a database of 1,800 benign and malignant lesions.[10] It can analyse changes in colour, pattern and size. Studies of its use have reported performance to be the same or better than that of trained clinicians, with a 91% sensitivity (95% CI: 86%–96%) and a 65% specificity (95% CI: 64%–72%).[11]

Digital dermatoscopy computer analysis

MelaFind® is a multispectral, digital non-polarised light dermatoscope. White light from a stable source, which has been filtered, is transmitted to the skin by fibre optics controlled by the computer. A charge-coupled device detects ten different, narrow-spectrum wavelength bands from 430 nm (the blue end of visible light) to 950 nm (infrared). Automatic image analysis and statistical pattern recognition identifies lesions to be considered for biopsy, to rule out melanoma. A prospective multicentre study on the performance of MelaFind reported a 98% sensitivity for melanoma, which is impressive – if only the aver-

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age specificity of 9.6% could be explained better in the paper.[12]

DB-MIPS

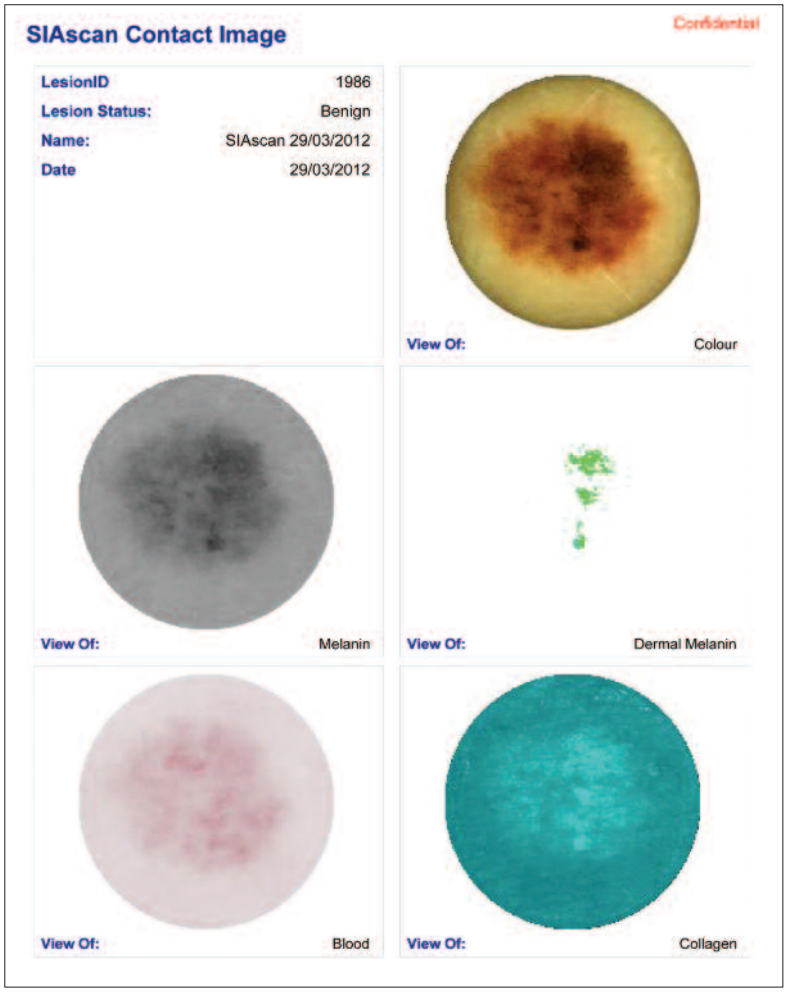
The DB-MIPS system (BIO MIPS Engineering), developed in Italy, evaluates 35 variables from dermatoscopic images producing geometry, colour, colour distribution and texture parameters. A three-centre analysis of this image analysis tool showed a sensitivity of 90–95% between the three centres, while specificity varied between 79.6% and 93.3% when applied to analysis of excised lesions suspected for melanoma.[13]

SIAscope™ and MoleMate®

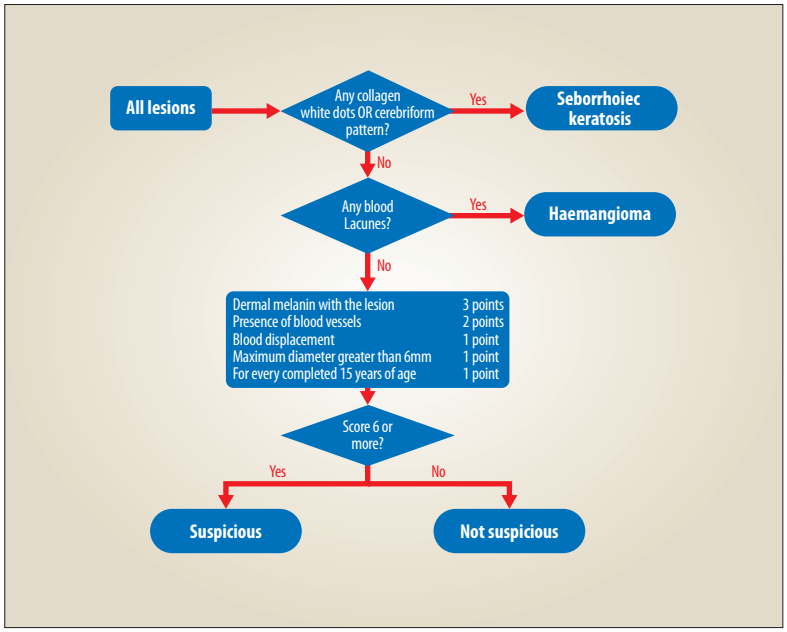
The SIAscope utilises the images acquired in the same way as a polarised light dermatoscope, but displays, in addition to the dermatoscopic image, views that split off the component parts made by each 'chromophore' in the skin, according to its absorption or reflection of light within the 400 nm to 1,000 nm range. Separate melanin images, including melanin located in the dermis, blood and collagen views, are displayed. Figure 4 shows complete images from SIAscopy, which includes a dermoscopy view, SIAgraphs to show total melanin, melanin in the dermis, the blood view and the collagen view. Other than asymmetric dermal melanin, none of the other features seen in invasive melanoma are present here (no blood displacement or collagen hole). The ability of the SIAgraph to pull out melanin when it resides in the dermis correlates with the presumed blue/white structures seen in dermal melanin, and supports the dermatoscopic decision-making that these are indeed suspicious features worthy of referral. Although the lesion is suspicious, the SIAgraphs suggest it is not melanoma. Nevertheless, with the history of change in a patient with previous melanoma, unable to monitor the lesion as it is on the back, referral for consideration of biopsy is indicated overall.

Moncrieff *et al* found that the presence of melanin in the dermis is very sensitive for melanoma, but it is not specific. However, combining features of blood displacement with an erythematous blush, and the presence of a hole in the collagen view, increases the sensitivity for melanoma to 82.7% and specificity to 80.1%.[14] Haniffa *et al* showed that the system performed almost as well as a dermatologist with 20 years' experience.[15]

Encouraged that the SIAscope could potentially work as well in non-expert hands as in those of a clinician, an algorithm, MoleMate®, was derived to try and aid descrimination of non-melanocytic from melanocytic lesions, and also to produce a risk-analysis score (see Figure 5). Features to help separate haemangiomas and seborrhoeic keratoses are highlighted in certain views, and the risk analysis is performed based on weighted criteria, with dermal melanin being the most important. Menzies *et al* had also found that when SolarScan was applied to all lesions, it underperformed when used on seborrhoeic keratoses, haemangiomas



■ **Figure 4.** Complete images from SIAscopy



■ **Figure 5.** The MoleMate algorithm

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and dermatofibromas – a recurring theme, thwarting artificial intelligence approaches.[11]

The MoleMate algorithm has recently been tested in the UK, in the only published randomised controlled trial of a device for melanoma detection at primary care level. Standard best practice (the seven-point checklist) was compared with best practice with the addition of scoring the lesions with the MoleMate algorithm. No difference was found in sensitivity or negative predictive value (NPV) (MoleMate versus best practice: sensitivity 98.5% versus 95.7%, p=0.26; NPV: 99.6% versus 99.2%, p=0.46). MoleMate showed a significantly lower specificity with a higher proportion of lesions referred (MoleMate versus best practice: specificity 84.4% versus 90.6%, p<0.001; lesions referred: 29.8% versus 22.4%, p=0.001). This paper seemed to report better outcomes than previously reported for general practice, in both arms.[16]

Very few studies have been based on the real world of primary care

High-resolution ultrasound

Acoustic pulses are generated and echoes (returning waves) are detected and displayed visually. High-frequency ultrasound has short wavelengths and, typically, in dermatology, a frequency >20 MHz is used in the analysis of lesions near the skin surface, while a frequency of 50–100 MHz is required for melanocytic lesions. High-resolution ultrasound has not been shown to be diagnostically useful, but may be of use in assessing lesion thickness when planning initial surgery.

Key points

- The National Institute for Health and Clinical Excellence recommends that any lesion that cannot be diagnosed as definitely benign should be referred to an expert for urgent assessment.
- While dermatoscopy is superior in diagnosing melanoma when compared with the unaided eye, it is not recommended for untrained users. An online dermatoscopy training tutorial has been shown to be of some benefit in training primary care practitioners in its use.
- The introduction of camera attachments for mobile phones, as well as smartphone apps, has introduced the potential for better diagnosis in the primary care setting.
- While digital dermatoscopy performs well in detecting present melanoma, it under- performed in terms of reaching conclusions about benign lesions.

Confocal scanning laser microscopy

A small volume of laser light in the visible, or near infrared, spectrum is focused on a small point within the skin and carefully filtered on its way back to a photodetector to generate images for display. An array of face-on slices from the *stratum corneum* to the upper papillary dermis is created. Algorithms to separate out non-melanocytic lesions have to be used and the interpretation is akin to histopathological examination. In its current research setting, an impressive overall sensitivity of 88.15% and overall specificity of 97.60% for melanoma are quoted and encouraging figures have been recorded even for the elusive amelanotic melanoma.[17] Currently, the technology is expensive and bulky and interpretation requires skill, but that is not to say that in a few years this may not be as available as ultrasound scanning is now, once its place has been established.

Conclusion

Walter *et al* have concluded, from the MoleMate study, that the systematic application of best practice guidelines should be the paradigm for management of suspicious pigmented lesions in primary care, these being the rigorous use of the seven-point checklist.[16] The high sensitivity for primary care practitioners in this study has not been reported elsewhere. The study design had patients whose lesions could not immediately be classified as benign return for a dedicated appointment, with one investigator for each practice. Just this step alone to enable careful and detailed assessment may have been important in enforcing best practice.

Dermatoscopy has a learning curve (even for the three-point dermatoscopy system), but if an individual in each practice becomes expert in this field, by either attending dedicated courses or taking part in online dermatoscopy training, it is likely that, once a level of experience has been reached, the positive predictive value for detecting benign lesions will increase. This will result in fewer onward referrals and biopsies, while the sensitivity for melanoma detection will probably increase with experience, towards that of acknowledged experts (around 95%).

Digital dermatoscopy systems have the advantage of producing an archived image for comparison and analysis by artificial intelligence methods. So far, artificial intelligence approaches the sensitivity of expert clinicians at the expense

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of specificity and very few studies have been based on the real world of primary care, with its preponderance of benign lesions – many of which are not melanocytic.

Where to in the future? An image taken with a digital dermatoscope, SIAscope, or even an iPhone with a dermatoscopic attachment, can now be emailed or uploaded for a second opinion from an expert; effectively accessing intelligence that is not so 'artificial'. NICE insists that lesions should be referred under the two-week cancer pathway for an opinion. With discouragement of review appointments in secondary care, there is a tendency to perform diagnostic biopsy more frequently than before. Used cautiously, as part of a planned service, a telemedicine approach to triage lesions that should be assessed in secondary care could have positive health economic benefits by reducing the costs to primary care, thus freeing precious space in overburdened dermatology clinics for more medically complex advice and interventions[18] ■

Declaration of interest

Per Hall has been involved in many studies evaluating image processing applications for the detection of melanoma, including the development and assessment of SIAscopy and the MoleMate algorithm. He has never had any financial links to any of the companies involved with the development of SIAscopy (the intellectual property for SIAscopy belonged to Astron Clinica, then Biocompatibles and is currently owned by MedX, Canada). He is affiliated with SkinHealth UK (www.skinhealthuk.com), a commercial organisation providing health screening and education for corporate clients and the general public, via a telemedicine approach where he is the clinical lead for skin.

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PRESCRIBING INFORMATION

PRESCRIBING INFORMATION: Protopic® 0.03% ointment (tacrolimus monohydrate) **ACTIVE INGREDIENT** Protopic® 0.03% ointment (1g) contains 0.3mg of tacrolimus as tacrolimus monohydrate (0.03%). **THERAPEUTIC INDICATIONS** Protopic® 0.03%: - treatment of moderate to severe atopic dermatitis in children (2 years of age and above) who failed to respond adequately to conventional therapies such as topical corticosteroids. - treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids. Protopic® 0.03%:- maintenance treatment of moderate to severe atopic dermatitis for prevention of flares and prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (i.e. occurring 4 or more times per year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected). **DOSAGE AND METHOD OF USE** Protopic® 0.03% should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis. Protopic® 0.03% can be used for short-term and intermittent long-term treatment. Treatment should not be continuous on a long term basis. Protopic® 0.03% should be applied as a thin layer to affected or commonly affected areas of the skin and may be used on any part of the body, including face, neck and flexure areas (except eyes and mucous membranes). Protopic® 0.03% should not be applied under occlusion. Protopic® 0.03% is not recommended for use in children below the age of 2 years until further data are available. Specific studies have not been conducted in elderly patients. However clinical experience has not shown the necessity for any dosage adjustment. Treatment of flares: Protopic® 0.03% treatment should begin at the first appearance of signs and symptoms. Each affected region of the skin should be treated with Protopic® 0.03% until lesions are cleared, almost cleared or mildly affected. Thereafter, patients are considered suitable for maintenance treatment (see below). At the first signs of recurrence (flares) of the disease symptoms, treatment should be re-initiated. *General considerations for treatment of flares:* Use in children (2 years of age and above) Treatment with Protopic® 0.03% should be started twice a day for up to three weeks. Afterwards the frequency of application should be reduced to once a day until clearance of the lesion. Generally, improvement is seen within one week of starting treatment. If no signs of improvement are seen after two weeks of treatment, further treatment options should be considered. Maintenance of flare-free intervals: Protopic® 0.03% should be applied once a day twice weekly (e.g. Monday and Thursday) to commonly affected areas to prevent progression to flares. Between applications there should be 2-3 days without Protopic® 0.03% treatment. If signs of a flare reoccur, twice daily treatment should be re-initiated. After 12 months, a review of the patient's condition should be conducted by the physician and a decision taken whether to continue maintenance treatment. In children, this review should include suspension of treatment to assess the need to continue this regimen and to evaluate the course of the disease. **UNDESIRABLE EFFECTS** Very common: Burning sensation (which tends to resolve within one week of starting treatment), pruritus. Common: Sensation of warmth, erythema, pain, irritation, paraesthesia and rash skin irritation after consumption of an alcoholic beverage). Patients may be at an increased risk of herpes viral infections (herpes simplex [cold sores], eczema herpeticum, Kaposi's varicelliform eruption) and folliculitis. Uncommon: acne. During post-marketing experience: Rosacea and application site oedema. Also, cases of malignancies, including cutaneous (i.e. cutaneous T Cell lymphomas) and other types of lymphoma, and skin cancers, have been reported in patients using tacrolimus ointment. Application site impetigo and application site infections occurred more frequently in a study of maintenance treatment in adults and children. Prescribers should consult the summary of product characteristics in relation to other side effects. **PRECAUTIONS FOR USE** Exposure of the skin to sunlight should be minimised and the use of ultraviolet (UV) light from a solarium, therapy with UVB or UVA in combination with psoralens (PUVA) should be avoided during use of Protopic® 0.03%. Patients should be advised on appropriate sun protection methods, such as minimisation of the time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing. Protopic® 0.03% ointment should not be applied to lesions that are considered to be potentially malignant or pre-malignant. The development of any new change different from previous eczema within a treated area should be reviewed by the physician. Protopic® 0.03% is not recommended in patients with skin barrier defect, such as Netherton's syndrome, lamellar ichthyosis, generalised erythroderma or cutaneous Graft Versus Host Disease. Care should be exercised if applying Protopic® 0.03% to patients with extensive skin involvement over an extended period of time, especially in children. Patients, particularly paediatric patients should be continuously evaluated during treatment with respect to the response to treatment and the continuing need for treatment. After 12 months this evaluation should include suspension of Protopic® 0.03% treatment in paediatric patients. The potential for local immunosuppression (possibly resulting in infections or cutaneous malignancies) in the long term (i.e. over a period of years) is unknown. Protopic® 0.03% contains the active substance tacrolimus, a calcineurin inhibitor. In transplant patients, prolonged systemic exposure to intense immunosuppression following systemic administration of calcineurin inhibitors has been associated with an increased risk of developing lymphomas and skin malignancies. In patients using tacrolimus ointment, cases of malignancies, including cutaneous (i.e. cutaneous T Cell lymphomas) and other types of lymphoma, and skin cancers have been reported. Protopic® 0.03% should not be used in patients with congenital or acquired immunodeficiencies or in patients on therapy that causes immunosuppression. Patients with atopic dermatitis treated with Protopic® 0.03% have not been found to have significant systemic tacrolimus levels. Lymphadenopathy was uncommonly (0.8%) reported in clinical trials. The majority of these cases related to infections (skin, respiratory tract, tooth) and resolved with appropriate antibiotic therapy. Patients who receive Protopic® 0.03% and who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves. Lymphadenopathy present at initiation of therapy should be investigated and kept under review. In case of persistent lymphadenopathy, the aetiology of the lymphadenopathy should be investigated. In the absence of a clear aetiology for the lymphadenopathy or in the presence of acute infectious mononucleosis, discontinuation of Protopic® 0.03% should be considered. The effect of treatment with Protopic® 0.03% on the developing immune system of children aged below 2 years has not yet been established. Before commencing treatment with Protopic® 0.03%, clinical infections at treatment sites should be cleared. Emollients should not be applied to the same area within 2 hours of applying Protopic® 0.03%. Concomitant use of other topical preparations has not been assessed. There is no experience with concomitant use of systemic steroids or immunosuppressive agents. Protopic® 0.03% should be used with caution in patients with hepatic failure. Protopic® 0.03% should not be used during pregnancy unless clearly necessary and is not recommended when breast-feeding. Protopic® 0.03% is unlikely to have an effect on the ability to drive or use machines. **CONTRAINDICATIONS** Hypersensitivity to macrolides in general, to tacrolimus or to any of the excipients. **INTERACTIONS** Paediatric population:- An interaction study with protein-conjugated vaccine against Neisseria menigitidis serogroup C has been investigated in children aged 2-11 years. No effect on immediate response to vaccination, the generation of immune memory, or humoral and cell-mediated immunity has been observed. Systemically available tacrolimus is metabolised via the hepatic Cytochrome P450 3A4. The possibility of interactions cannot be ruled out and the concomitant systemic administration of known CYP3A4 inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. **PACKAGE SIZES** Prices exclude VAT: Protopic® 0.03% ointment £19.44 (30g tube), £35.46 (60g tube) **LEGAL CATEGORY**: POM. **MARKETING AUTHORISATION NUMBERS** Protopic® 0.03% ointment EU/1/02/201/001-2. **FURTHER INFORMATION AVAILABLE FROM**: Astellas Pharma Ltd, 2000 Hillswood Drive, Chertsey, Surrey, KT16 0RS. UK. **DATE OF REVISION**: September 2012 **FOR FULL PRESCRIBING INFORMATION REFER TO THE SUMMARY OF PRODUCT CHARACTERISTICS.**

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard
Adverse events should also be reported to Astellas Pharma Ltd.
Please contact 0800 783 5018

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217 days without a major eczema flare? Here's to a (Great) British summer.

Paediatric patients (≥2–15 years) with moderate-to-severe atopic dermatitis (AD) treated proactively twice-weekly with 0.03% Protopic were free from major flare for a median of 217 days, compared with 36 days for those receiving Protopic flare treatment alone[1,2*]

Exposure of the skin to sunlight should be minimised and patients advised on appropriate sun protection methods, such as minimisation of the time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing[2]

astellas

* Proactive Protopic use for flare prevention of moderate-to-severe AD in patients experiencing >4 flares/year that have previously responded to Protopic after they have failed to adequately respond to conventional therapies, such as topical corticosteroids[2]

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1. Reitamo S and Allsopp R. *J Dermatol Treat* 2010; **21**: 34–44.

2. Protopic 0.03% Summary of Product Characteristics, August 2012.

Prescribing information can be found on the adjacent page

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