Clinical review

Recent advances

Dermatology

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Dermatology is a diverse specialty. It is one of the few areas of medicine in which a specialist can be both physician and surgeon, treating malignant and non-malignant disease in a population ranging from infants to adults. It is constantly evolving. In recent years, dermatology has incorporated techniques and treatments from other disciplines, such as genetic studies and the use of immunosuppressive agents, and pioneering work in the rapidly expanding area of laser therapy has broadened the diagnostic and therapeutic horizon. Advances in the understanding of dermatological conditions have allowed dermatologists to refine treatments.

Methods

The recent advances discussed in this review are common knowledge among dermatologists. The choice of topics is personal and, after a review of the major dermatological journals, covers a selection of aetiological and therapeutic areas that are making a difference in practice now or are likely to do so in the very near future.

Lasers

Laser therapy in dermatology is expanding rapidly and can be used to treat vascular and pigmented lesions, to remove tattoos, for depilation, and for skin resurfacing. It is now possible to choose laser treatments based on a specific wavelength, pulse width, and fluency. This allows selective targeting and destruction of specific cellular and subcellular structures while the normal surrounding structures are spared thermal damage. Scarring and other complications are minimised.¹⁻³

Treatments available for tattoo removal had been limited by the likelihood of scarring.³⁻⁵ The new short pulsed laser treatments (including pulsed dye and Q switched ruby, Nd:YAG, and alexandrite lasers) which are now the preferred means of tattoo removal are based on the theory of selective photothermolysis. Thermal damage is localised by the choice of a wavelength that is selectively absorbed by the specific target chromophore and by delivering sufficient energy to damage the target within a pulse duration which is briefer than the time taken for the target to cool (thermal relaxation time).^{3,4} Proposed mechanisms for removing pigment include rephagocytosis of laser altered pigment particles and transepidermal

Summary points

Lasers are now used for depilation and for removing tattoos without leaving scarring

Photodynamic therapy is increasingly being used to treat skin tumours

Narrowband ultraviolet B light has largely replaced other forms of phototherapy for psoriasis and severe atopic dermatitis

Kaposi's sarcoma is associated with human herpesvirus 8

Better understanding of androgenetic alopecia has allowed the development of effective treatment with finasteride

More specific immunomodulatory drugs, including those adapted from other areas of medicine, are now being used in dermatology

elimination via the scale crust that forms.³ Patients may require four to eight treatments every six to eight weeks to achieve maximum improvement, and the response of professional tattoos may be slower and less complete.^{1,6}

The Q switched ruby, Nd:YAG, and alexandrite lasers have also been used to treat disorders of cutaneous pigmentation such as solar lentigines, café au lait macules, ephelids, post-inflammatory pigmentation, melasma, and naevus of Ota.^{5,6}

Although laser assisted epilation (or phototricholysis) is not considered a permanent way of removing hair, some patients will achieve a long term reduction in hair density after a single treatment.^{7,8} Lasers with wavelengths of 600-1100 nm (such as the ruby, alexandrite, Nd:YAG, and diode) penetrate deeply and are absorbed by eumelanin in the hair shaft and follicle, which is thought to be the target chromophore.¹ Relatively long pulses are used to create sufficient damage to the follicles. The predominant effects are photomechanical (shock waves) with nanosecond domain Q switched pulses and photothermal (heat) with millisecond domain pulses.⁸ These lasers work best on pale skin with pigmented hairs.

Fig 1 Nodular basal cell carcinoma may be treated with photodynamic therapy in sites where surgery is likely to be disfiguring

Photodynamic therapy

In general, surgical excision is the most effective and preferred treatment for primary skin cancer. However, photodynamic therapy is increasingly being used to manage many epithelial tumours, including those of the skin. After the selective uptake and retention of an exogenously administered or endogenously formed photosensitiser within tumour tissue, exposure to light of a specific wavelength results in intracellular activation of the photosensitiser. This leads to cell death by the formation of radical products (type I mechanism) or intracellular singlet oxygen (type II mechanism).⁹⁻¹²

Topically applied aminolaevulinic acid (converted intracellularly to predominantly protoporphyrin IX) and systemically administered photosensitisers have been used to treat cutaneous neoplasms.¹⁰⁻¹³ Irradiation with the appropriate wavelength of light is performed when an optimal ratio of photosensitiser in tumour tissue compared with non-tumour tissue is reached. This tends to occur four to six hours after topical aminolaevulinic acid is applied or 96 hours after systemic photosensitisers are given intravenously.¹⁰

The highest response rates so far have been seen with treatment of solar keratoses. Superficial basal cell carcinoma, nodular basal cell carcinoma (fig 1), Bowen's disease, squamous cell carcinoma, mycosis fungoides, psoriasis, and Kaposi's sarcoma have also been treated in this way, but further work is necessary to compare the efficacy and convenience of photodynamic therapy with conventional forms of treatment for these conditions. The efficacy of photodynamic treatment may be increased by adjuvant treatments. Photodynamic therapy is currently not suitable for the treatment of morphoeic basal cell carcinoma.¹⁰⁻¹²

Irradiation of sensitised skin causes erythema and a mild or occasionally painful burning sensation within the treatment field. Erythema and mild oedema develop within 24 hours. Selective tumour necrosis occurs within two days, and there may be milder erythema of adjacent normal tissue. Increased light intensity causes a less selective reaction, and adjacent normal tissue is more likely to develop necrosis. Healing is usually complete within four to six weeks. Cosmetic results are considered as good or better than other treatments, including surgery and cryotherapy.¹⁰⁻¹¹

Narrowband ultraviolet B

Narrowband ultraviolet B light has now largely superseded broadband ultraviolet B in treating psoriasis (fig 2) as it induces longer remissions and causes fewer burns.¹⁴⁻¹⁵ It has also been shown to be an effective steroid sparing treatment for chronic severe atopic dermatitis.¹⁶ As narrowband ultraviolet B has fewer of the shorter erythrogenic wavelengths and the ultraviolet A components, it may induce a photoprotective effect for the predominantly ultraviolet A induced photosensitivity disorders while posing a lower risk of erythema and exacerbation. Narrowband ultraviolet B is as effective as psoralens plus ultraviolet A (PUVA) in the prophylactic management of polymorphic light eruption and is of value in the management of actinic prurigo, solar urticaria, and cutaneous porphyria.¹⁶

The narrowband TL-01 lamp, with an emission spectrum of predominantly 311-313 nm, was developed as a result of therapeutic wavelength dependency studies of psoriasis.¹⁴⁻¹⁵ These showed that much of the shorter wavelength component of conventional broadband ultraviolet B light was ineffective.

Long term exposure to ultraviolet light increases the risk of photoageing and cutaneous malignancy, and in mice narrowband ultraviolet B is two to three times more carcinogenic per minimal erythema dose than broadband ultraviolet B. However, the average number of narrowband ultraviolet B minimal erythema doses required to induce remission in psoriasis is less than a third of the number required with broadband ultraviolet B, suggesting similar or lower tumour risk.¹⁵⁻¹⁶

Narrowband ultraviolet B can be given to children and during pregnancy.¹⁶ In general, treatment is given three times per week. This tends to reduce the total number of exposures and the cumulative dose and, it is hoped, the long term risk. Treatment is stopped when the patient's condition has resolved, and no maintenance treatment is given.

Fig 2 Ultraviolet treatment for psoriasis

Fig 3 Kaposi's sarcoma associated with HIV/AIDS

Kaposi's sarcoma and human herpesvirus 8

The recently discovered Kaposi's sarcoma associated herpesvirus or human herpesvirus 8 has been detected in all forms of Kaposi's sarcoma, including the classic sporadic form (fig 3), the form associated with AIDS, the form not associated with HIV immunosuppression, the African endemic form, and the rare familial forms. It has therefore been regarded as a causative factor in the pathogenesis of Kaposi's sarcoma. Human herpesvirus 8 has also been associated with body cavity based lymphoma (often coinfecting with Epstein-Barr virus) and multicentric Castelman's disease, which are also commonly associated with HIV infection. Human herpesvirus 8 contains three potential oncogenes that can transform cell lines in vitro. Human herpesvirus 8 DNA has been localised to the nuclei of tumour cells within Kaposi's sarcoma lesions, and the virus has been detected in peripheral blood mononuclear cells in over half of HIV positive patients with Kaposi's sarcoma.¹⁷⁻¹⁹

Between 70% and 100% of patients with Kaposi's sarcoma have antibodies to human herpesvirus 8 (compared with 1%-5% of the general population). Seroconversion may occur several months before the clinical appearance of the disease, supporting a causative role for herpesvirus in Kaposi's sarcoma. In countries such as southern Italy and Uganda, where classic and endemic Kaposi's sarcoma are relatively common, human herpesvirus 8 is also more widespread.^{17 18}

Androgenetic alopecia

Androgenetic alopecia (or male pattern baldness) begins with recession of the frontal hairline. This is followed by thinning over the vertex and then, eventually, complete loss of hair over the crown. It is partially mediated by circulating and locally produced androgens, including testosterone and 5-dihydrotestosterone, combined with a genetic susceptibility, possibly inherited in an autosomal dominant fashion with variable penetrance.²⁰ Men who have been castrated before puberty and homozygotes for 5 α -reductase type II deficiency do not develop androgenetic alopecia.^{20 21} 5 α -Reductase is the enzyme that converts testosterone to 5-dihydrotestosterone. On the scalp of patients who are predisposed to the condition, androgens lead to miniaturisation, a switch from terminal to vellus or vellus-like follicles, and a reduction in the duration of anagen.^{20 22} The concentration of androgen receptor and 5 α -reductase activities in frontal hair

follicles is greater than in occipital follicles.²³ Higher activities of aromatase, a bifunctional enzyme involved in converting testosterone to oestradiol, are found in occipital hair follicles.²³ This may explain the loss of hair in the frontal area in androgenetic alopecia, while occipital hair is retained. In women, in whom androgenetic alopecia expression is less severe and often spares the frontal hair line, lower concentrations of androgen receptors and 5 α -reductase activities are found in the frontal hair follicles, and aromatase activities are higher.²³

Finasteride is a 5 α -reductase inhibitor. Its use results in decreased circulating and scalp concentrations of 5-dihydrotestosterone and a compensatory rise in testosterone and gonadotrophin values.^{20 21} The androgen receptor is not affected by finasteride.²⁰ Further hair loss is prevented in most patients treated with finasteride. About half of men achieve some regrowth, and in about a third, after two years of continuous use, this is considered cosmetically important.²¹ To date, studies have examined the effect only at the vertex, where the benefit is greatest. Less clinically dramatic but statistically significant improvement in hair counts also occur at the frontotemporal scalp margin, indicating that the progression of hair loss in this region may at least be prevented.²⁰ Although regrowth may be seen as early as three months, patients should be encouraged to take finasteride for two years before evaluation.^{21 22} The prevention of further loss and the likelihood of regrowth do not seem to correlate with the grade of androgenetic alopecia. If treatment is successful it should be continued indefinitely, as the balding process continues when it is stopped.²²

The most common side effects, which occur in less than 2% of men, are erectile dysfunction, diminished libido, and decreased ejaculate volume. These effects are reversible and tend to be less of a problem over time if the patient continues taking the drug.^{21 22} To date, this agent has not been shown to be effective in treating female androgenetic alopecia.²⁰

Immunomodulating agents

There is a continual search in dermatology for more selective anti-inflammatory drugs to replace broad spectrum steroids. Tacrolimus (FK506), which is related to cyclosporin, is a powerful immune suppressor that was introduced to reduce organ transplant rejection. Like cyclosporin, it has been used systemically to treat psoriasis, atopic dermatitis, and pyoderma gangrenosum.²⁴

Unlike cyclosporin, tacrolimus seems to be effective when applied topically.²⁵ Initial open trials suggest that over 90% of children and adults rapidly achieve at least good improvement of atopic dermatitis. There is no systemic accumulation. Adverse effects occur in about half but are transient and are predominantly burning and erythema at the application site.²⁵

Mycophenolate mofetil, which was also used predominantly for the prophylaxis of allograft rejection, was originally synthesised to increase the bioavailability and immunosuppressive properties of the active metabolite, mycophenolic acid, to which it is rapidly hydrolysed and transformed in the liver. Mycophenolic acid is in turn metabolised in the liver and excreted in the urine. β -D-Glucuronidase in the epidermis and other

tissues is able to convert the inactive glucuronide back to the active form.²⁶⁻²⁸ By non-competitively inhibiting the de novo pathway of purine synthesis, mycophenolic acid produces a potent cytostatic effect in nucleic acid synthesis of both T and B lymphocytes, which results in inhibition of lymphocyte proliferation and antibody formation. Leucocyte recruitment and glycation of lymphocyte glycoproteins involved in adhesion to endothelial cells are also blocked.²⁶⁻²⁸

Mycophenolate mofetil is reported to be antibacterial, antifungal, antiviral, and immunosuppressive. It has been used systemically in the treatment of psoriasis, pyoderma gangrenosum, bullous pemphigoid, pemphigus vulgaris, and systemic vasculitis.²⁶⁻²⁸ The usual dosage is 1 g orally twice daily. Side effects such as gastrointestinal intolerance and minor urinary symptoms are usually mild and are predominantly dose dependent. Bone marrow suppression with mild to moderate leucocytosis and anaemia is seen in less than 5% of patients. Early reports suggesting an increased risk of carcinogenicity, especially lymphoma, have not been borne out in subsequent studies.²⁷ Topical mycophenolic acid is being assessed for its value in inflammatory skin conditions such as eczema and psoriasis.

Imiquimod induces production of interferon alfa, along with pro-inflammatory cytokines such as interleukin 1, interleukin 6, interleukin 8, and tumour necrosis factor alpha. It is an immune enhancing agent with antiviral and anti-tumour effects. Interferon alfa has been shown to be an effective treatment for several cutaneous conditions, including anogenital warts and non-melanoma skin cancer. However, it is not absorbed after topical application and requires intralesional injections. Imiquimod is applied topically, is well absorbed, and induces local interferon alfa.²⁹

Imiquimod cream (5%) applied three times per week eradicates about 50% of anogenital warts. The recurrence rate is the same as placebo. The most common side effect is local inflammation.²⁹ Trial applications of 1% imiquimod cream three times a day for five days a week for the treatment of molluscum contagiosum resulted in resolution in over 80% of patients and lesions. There were no adverse effects.³⁰ The potential of imiquimod in the treatment of cutaneous malignancy is the subject of current therapeutic trials.

The future

The important advances in dermatology touched on in this review illustrate some of the ways in which dermatology has exploited advances in molecular biology, pharmacology, and physical therapeutic techniques, permitting improved patient management. In the future, detailed epidemiological studies will enable us to recognise who is at risk of particular dermatological conditions. Establishment of familial tendencies will allow more detailed genetic and molecular biological investigation. With time, improved understanding of the genetic basis and molecular biology of skin disease will result in current empirical treatments becoming more specific to the underlying abnormality.

Competing interests: None declared.

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Electronic sources of dermatological information

Dermatology Online Journal	tray.dermatology.uiowa.edu/home.html
Internet Dermatology Society	www.telemedicine.org
RxDerm-L	listpro@ucdavis.edu (email)
Tumours of the skin, University of California at Davis	www.ucdavis.edu-huntley/tumors/tradition/tumors.html
Dermatology online atlas	www.derma.med.uni-erlangen.de/index_e.htm
Dermatology atlas	www.meddean.luc.edu/lumen/medEd/medicine/dermatology/melton/atlas.htm
Skin cancer and benign tumor image atlas	www.meddean.luc.edu/lumen/medEd/medicine/dermatology/content.htm
Dermatology image bank	www.tmc.edu.tw/medimage/derma_bank/default_eng.htm
Contact dermatitis	telemedicine.org?contact.htm
DermNet (atlas and information)	www.dermnet.org.nz/dna2a.html
Virtual Dermatology (case directory)	erl.pathology.iupui.edu/cases/dermcases/dermcases.cfm
Skindex-case directory (news, reviews, treatment trends, meeting reports, CME, case reports, disease descriptions, atlas, Q&A site)	www.skindex.com/

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