

Therapeutic Update on Seborrheic Dermatitis

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ABSTRACT

Seborrheic dermatitis is a recurrent, usually mild, skin disorder with typical clinical manifestations. As it most frequently involves exposed areas, such as the face and scalp, patients seek advice from a dermatologist in order to control their disease. This article will review the available treatments for this common dermatologic problem.

Key words: antifungals, calcineurin inhibitors, corticosteroids, lithium salts, metronidazole, phototherapy, seborrheic dermatitis, zinc pyrithione

Seborrheic dermatitis is a chronic mild skin disorder that characteristically presents as sharply demarcated red patches and plaques with greasy scales in areas with increased density of sebaceous glands, namely the scalp, face, upper trunk, and flexures. It affects approximately 3-5% of the population, with a predilection in men.¹ An even higher incidence can be found amongst patients with HIV infection, Parkinson's disease, and several other medical conditions.¹ There is still debate as to whether infantile seborrheic dermatitis represents a distinct dermatitis.

The pathogenesis of the disease remains controversial. The role of *Malassezia* spp. carriage is not clear. However, the number of yeasts decreases with antimycotic treatment, resulting in clinical improvement, and increases in periods of exacerbation.² Despite its name, sebum excretion in patients with seborrheic dermatitis is not significantly increased when compared with controls. *Malassezia* metabolism alters sebum composition by consuming saturated fatty acids and releasing unsaturated fatty acids, which in turn promotes inflammation in susceptible individuals.³ It has also been proposed that *Malassezia* spp. induce cytokine production by keratinocytes,⁴ while studies on cellular immunity show contradictory results.^{5,6}

Patients should be informed that all available therapeutic modalities alleviate symptoms temporarily until the next relapse, which is typically followed by variable periods of remission. Affected individuals should avoid causing compounding irritation to active lesions, i.e., through the mechanical removal of scales and the use of potent keratolytic preparations. Daily cleansing of the skin and the use of emollients are beneficial.

Topical Therapies

Topical therapies are the mainstay of treatment as the condition is recurrent, usually mild, and responds well to these agents.

Antifungals

Since the first publication in 1984 on the use of ketoconazole in seborrheic dermatitis,⁷ several studies have validated its efficacy utilizing various vehicles of delivery (e.g., cream, foam, gel, and shampoo).⁸⁻¹⁰ Ketoconazole shampoo 2% is superior to 1%¹¹ and can be used once-weekly as maintenance therapy for scalp seborrheic dermatitis.¹⁰

Another topical azole, bifonazole 1% cream, is likewise effective and provides the additional advantage of once-daily application. It has also been tried successfully in combination with 40% urea for scalp seborrheic dermatitis.¹² Bifonazole shampoo used 3 times weekly was significantly more beneficial than placebo in a randomized, double-blind study of 44 patients.¹³ Miconazole can also be used either alone or in combination with hydrocortisone.¹⁴

Ciclopirox has both antifungal and anti-inflammatory properties.¹⁵ Ciclopirox 1% cream is superior to placebo for facial seborrheic dermatitis.¹⁶ The response rates appear to be dose-dependent, with higher concentrations (1% vs. 0.1% or 0.3%) and more frequent use yielding better results.^{17,19} Combinations of ciclopirox 1.5% shampoo with salicylic acid 3% or zinc pyrithione 1% are also effective.^{19,20} Statistical non-inferiority of ciclopirox in comparison with ketoconazole has been demonstrated.²¹

Corticosteroids

For severe seborrheic dermatitis, low- or medium-potency topical corticosteroids can be used when beginning

treatment, either alone or in combination with an antifungal agent, to limit inflammation. Prolonged and/or frequent use should be avoided due to their well known associated risks (e.g., atrophy, telangiectasias, hypertrichosis, and perioral dermatitis). In a double-blind controlled study, 70 seborrheic dermatitis patients were treated with either miconazole 2% and hydrocortisone 1% in combination, miconazole 2%, or 1% hydrocortisone. Patients in both miconazole-containing treatment arms showed significant improvement when compared with those who received hydrocortisone 1% cream as prophylactic therapy.¹⁴ Miconazole treatments also lowered the number of *Malassezia* spp. yeasts.¹⁴ Double-blind comparative studies have found that hydrocortisone cream is not superior to ketoconazole 2% cream in improving seborrheic dermatitis symptoms, as significantly higher reductions in the number of *Malassezia* spp. were observed with ketoconazole, when compared with hydrocortisone.²² Ketoconazole 2% foaming gel was found to be superior to betamethasone dipropionate 0.05% lotion in reducing symptoms and lowering the number of *Malassezia* spp.²³

Zinc Pyrithione

Zinc pyrithione 1% shampoo in comparison with ketoconazole 2% shampoo has produced inferior results, whereas selenium sulphide exhibited similar efficacy.^{24,25}

Metronidazole

Topical metronidazole 0.75% gel for seborrheic dermatitis has been evaluated in only a limited number of double-blind studies with contradictory results. In two trials, metronidazole showed greater efficacy over placebo²⁶ and was equally effective as ketoconazole 2% cream,²⁷ while in two other studies it was not superior to placebo.^{28,29}

Lithium Salts

Both lithium succinate and lithium gluconate have demonstrated effectiveness in treating seborrheic dermatitis, probably due to their anti-inflammatory effects. Lithium succinate 8% ointment was investigated twice-daily (for a total of 8 weeks) and showed significantly greater efficacy than placebo.³⁰ It has also been used successfully in HIV patients with facial seborrheic dermatitis.³¹ Lithium gluconate 8% ointment used twice-daily was tested in a multicenter, randomized, double-blind, placebo-controlled clinical trial in 129 patients.³² After 8 weeks, 29.1% in the lithium group and 3.8% in the placebo group had experienced complete remission. Lithium gluconate 8% ointment used twice-daily was 22% more effective than ketoconazole 2% emulsion used twice-weekly in a randomized study of 288 patients.³³

Calcineurin Inhibitors

In a randomized, double-blind, vehicle-controlled 4-week efficacy trial of twice-daily pimecrolimus 1% cream in 96 patients, topical calcineurin inhibitor (TCI) therapy was effective and well tolerated for the treatment of facial seborrheic dermatitis.³⁴ In two randomized clinical trials,^{35,36} pimecrolimus 1% proved to be equally effective as topical corticosteroids (hydrocortisone acetate 1% cream or

betamethasone 17-valerate 0.1% cream). Furthermore, pimecrolimus demonstrated additional benefits, such as longer periods of remission and milder relapses, when compared with betamethasone.³⁵ This TCI has also been tested against ketoconazole 2% cream in an open randomized study that showed comparable efficacy, but more frequent side-effects were reported with pimecrolimus treatment.³⁷ Topical tacrolimus 0.1% ointment was tried in an open-label 4-week randomized study against betamethasone 17-valerate lotion and zinc pyrithione 1% shampoo in 83 patients with seborrheic dermatitis of the scalp.³⁸ Tacrolimus ointment demonstrated greater prolonged efficacy than topical steroids, but exhibited shorter durability of improvement than zinc pyrithione shampoo. Due to the increased viscosity of the tacrolimus ointment, treatment was inconvenient to use on the scalp.

Coal Tar Shampoos

The beneficial effects of tar in seborrheic dermatitis may be attributed to its anti-proliferative and anti-inflammatory properties, antifungal action, and inhibition of sebum secretion.³⁹ In a randomized, double-blind parallel-group trial, treatment with 4% coal tar shampoo resulted in a significantly greater reduction in scalp seborrheic dermatitis, when compared with placebo, and the result was further enhanced when coal tar was combined with ciclopirox olamine.⁴⁰

Selenium Sulphide

In a randomized double-blind trial, selenium sulfide 2.5% was tested against ketoconazole 2% and placebo in 246 patients with moderate to severe dandruff.⁴¹ Both ketoconazole and selenium sulfide shampoos were effective, but ketoconazole was better tolerated.

Other Topical Treatments

There are scarce reports of successful treatment with benzoyl peroxide,⁴² azelaic acid,⁴³ 1 α -24 (R)-dihydroxycholecalciferol (tacalcitol) cream,⁴⁴ and MAS064D cream (a non-steroidal preparation containing multiple active ingredients that include emollients, anti-inflammatories, keratolytics, and an antimycotic).⁴⁵

Phototherapy

Ultraviolet B (UVB)

Patients often experience improvement during the summer. The direct inhibitive effect of UVA and UVB light on *Malassezia* yeasts cultured from the skin has been experimentally confirmed.⁴⁶ In an open prospective study, 18 patients with severe seborrheic dermatitis were treated with narrow-band UVB 3 times per week until clearance or upon completing 2 months of therapy.⁴⁷ The median number of treatment sessions was 23 and the median cumulative UVB dose was 9.8 J/cm². All patients responded well to therapy, especially those with widespread disease. The major limitations of UVB irradiation for seborrheic dermatitis are the frequent visits to a phototherapy unit, the rapid disease relapse appearing 2-6 weeks after treatment, and the risks

associated with exceeding the maximum lifetime allowable cumulative dose.

Psoralen plus Ultraviolet A (PUVA)

Five HIV patients who were administered PUVA treatment (30 to 262 J/cm² every 2-4 weeks) exhibited clearance of skin lesions, including seborrheic dermatitis.⁴⁸ This finding contradicts the report of 28 new cases of facial seborrheic dermatitis appearing during PUVA therapy in 347 patients with psoriasis.⁴⁹

Systemic Therapies

Oral Antifungals

Controlled studies of systemic antifungal therapy are limited. In a randomized, double-blind, placebo-controlled study, 174 patients with seborrheic dermatitis received either 250mg of terbinafine or placebo for 6 weeks.⁵⁰ Patients with facial lesions did not benefit from terbinafine, while patients with lesions in non-exposed areas receiving terbinafine showed significant improvement. Another placebo-controlled trial showed that terbinafine 250mg daily for 4 weeks was more effective than placebo.⁵¹ In a double-blind, placebo-controlled study of 63 patients receiving either oral fluconazole 300mg in a weekly single dose or placebo for 2 weeks, no statistically significant improvement was seen between treatment groups.⁵² Ketoconazole 200mg daily for 4 weeks was tried in 19 patients in a randomized, double-blind, placebo-controlled study; active treatment resulted in significant improvement.⁵³ Itraconazole given at an initial dose of 200mg daily for 1 week, followed by a maintenance single dose of 200mg every 2 weeks, was beneficial in an open non-comparative study of 60 patients with moderate to severe seborrheic dermatitis.⁵⁴

Conclusion

Topical antifungal therapy has proved to be effective in many studies, offering more frequent and sustained relapse-free periods, as compared with corticosteroids and without their untoward side-effects. Therefore, antimycotic agents may be considered first-line treatment for seborrheic dermatitis. Other topical agents with established efficacy can be used as complimentary therapy. UVB phototherapy should only be considered for severe and/or recalcitrant disease. Oral administration of antifungals is highly questionable, as treatment carries the potential risk of serious side-effects from repetitive use.

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Current Management of Actinic Keratoses

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ABSTRACT

An actinic keratosis (AK) is a pre-malignant cutaneous lesion that frequently manifests in sun-exposed areas of the skin as a small, rough, scaly erythematous papule. They are one of the most common presenting complaints for dermatologists. AKs should be treated due to their potential to progress into a squamous cell carcinoma (SCC). There are numerous treatments available for managing AKs including those broadly categorized as destructive, topical field, and procedural field therapies. The topical field therapies include 5-fluorouracil, imiquimod, and diclofenac gel. Recently, imiquimod 3.75% (Zyclara™) has been approved for the treatment of AKs on the face and scalp. It is a reasonable alternative to imiquimod 5%, as the approved indication includes a larger surface area for treatment, shorter duration course, and the potential for less severe local skin reactions. There is no widely accepted algorithm for the treatment of AKs, as comparative data is unavailable between all approaches. Therapy choices are guided by efficacy, adverse effects, cosmetic results, and patient compliance.

Key words: actinic keratosis, imiquimod, squamous cell carcinoma, skin cancer, Zyclara™

Actinic keratoses (AKs), or solar keratoses, are pre-malignant cutaneous lesions that predominantly manifest in sun-exposed areas. They are one of the most common pathologies seen by dermatologists, preceded only by acne vulgaris and dermatitis as more frequent complaints.¹ AKs are clinically relevant lesions due to their potential to progress into a squamous cell carcinoma (SCC).² Additionally, they are considered a risk factor for the subsequent development of melanoma and non-melanoma skin cancer (NMSC).

In the northern hemisphere, 11-25% of adults are believed to have at least one AK.³ These lesions are most commonly seen in the older fair-skinned population (Fitzpatrick skin phototypes I-III). Cumulative ultraviolet (UV) radiation exposure and older age are the most important risk factors for this condition. Individuals who are immunocompromised or have certain genetic syndromes, such as xeroderma pigmentosum and albinism, are at greater risk.

Pathophysiology

Grossman and Leffell² explain that UV radiation is involved in the pathogenesis of AKs through inducing cellular DNA mutations in the skin, which may affect cell proliferation genes, such as p53 and ras, or prompt evasion of apoptosis. Disruption of one of these genes may lead to the formation of atypical keratinocytes in the basal layer and development of an AK; all of these histopathologic changes are limited to the epidermis. The absence of further UV light exposure may result in resolution through repair mechanisms. However, additional UV light exposure may induce further DNA mutations, resulting in the development of an invasive SCC.

AKs typically manifest as small (1-3mm) erythematous scaly papules with a hyperkeratotic texture. As such, they are best identified with touch rather than visual inspection alone. AKs are characteristically distributed in sun-exposed areas, including the face, bald scalp, ears, neck, anterior chest, dorsal forearms, and dorsal hands. Surrounding areas

may show evidence of solar elastosis, such as telangiectasia, blotchy hyperpigmentation, and yellow discoloration of the skin.⁴ The clinical variants of actinic keratosis include the cutaneous horn, lichen planus-like keratosis, pigmented actinic keratosis, and actinic cheilitis.^{4,5} Over several years, these lesions can progress, becoming thicker and developing into a hypertrophic AK, Bowen's disease (SCC *in situ*), or an invasive SCC. Unfortunately, the stages of this biologic continuum are clinically indistinguishable and a biopsy should be performed if a SCC is suspected. However, a presentation that includes pain, pruritus, induration, larger size, rapid growth, ulceration, bleeding, or resistance to treatment may point towards a more sinister pathology (i.e., SCC).^{4,5}

The natural history of AKs is variable and unpredictable. The lesion can follow one of three paths: it can persist, regress, or transform into an invasive SCC. It is impossible to predict which path any given AK may take. The risk of a single lesion progressing from an AK to a SCC ranges from 0.025-16% per year.⁶ Nonetheless, it is recommended that all AKs be treated as there are no reliable clinical predictors to discern an AK from a SCC. If a SCC is missed, it may become locally invasive and destructive; these lesions are capable of metastases resulting in death.

Destructive Therapy

The most common therapies for individual AKs work destructively by physically removing the lesion. These should always be considered for isolated lesions or early presentations of AKs. Destructive therapies include liquid nitrogen cryotherapy, curettage with or without electrodesiccation, and shave excision. The main advantages of these procedures are that they are quick, procedurally simple, and provide adequate clearance of abnormal tissue. A major limitation of such targeted approaches is that they fail to address field cancerization.

Cryotherapy

Cryotherapy is the most commonly utilized technique, with liquid nitrogen being the most frequently selected cryogen. Applying cryotherapy to the affected area lowers the skin to temperatures that destroy atypical AK cells.⁷ This technique is ideal if lesions are scattered or limited in number, or for patients who are non-compliant with topical regimes.⁷ Reported cure rates range from 39-83%.⁸ Cryotherapy is advantageous in that it is generally well-tolerated and does not require local anesthetic, but downsides include pain during the procedure and frequent permanent hypopigmentation. Potential side-effects include blisters, scarring, textural skin changes, infection, and hyperpigmentation.

Curettage and Shave Excision

Curettage consists of using a curette to mechanically remove atypical cells. A shave excision using a surgical blade is another technique. These may be followed by electrocautery, which will destroy additional atypical cell layers as well as provide hemostasis. There are no studies documenting cure rates with these treatment modalities. These techniques are most appropriate for treating individual AKs, cases where a biopsy is required to rule out frank carcinoma, or for hypertrophic AKs that are refractory to other treatments. Potential side-effects include infection, scarring, anesthetic related side-effects, and dyspigmentation.

Topical Field Therapy

Commonly, physicians are faced with patients who are covered in actinic damage, a clinical scenario now described as field cancerization. This describes both clinical and subclinical lesions within a given anatomical region.⁹ For these patients, a different therapeutic approach, known as field therapy, is needed. The goal of field therapy is the eradication of both the clinically visible and subclinical AKs within the treatment area.

Topical 5-fluorouracil

The antimetabolite 5-fluorouracil (5-FU) was the first approved topical field therapy. Discovered serendipitously when AKs were noted to become inflamed and subsequently resolved in patients receiving systemic 5-FU as a chemotherapeutic agent, it was eventually designed into an effective topical formulation. It acts as a thymidylate synthase inhibitor by blocking a methylation reaction; this in turn disrupts DNA and RNA synthesis and effectively stops the growth of the rapidly proliferating or cancerous cells.¹⁰ As such, 5-FU preferentially targets the atypical cells over normal cutaneous tissue. The average cure rate is 62.5%,¹¹ but for optimal results full patient adherence is necessary. Interestingly, there is evidence showing concurrent treatment with topical tretinoin enhances the effectiveness of 5-FU.¹² All patients undergoing successful treatment should experience erythema, inflammation, and erosions. Commonly experienced side-effects include pain, pruritus, photosensitivity, and burning at the site of application. Additionally, topical 5-FU can exacerbate other pre-existing

cutaneous conditions, such as melasma or acne rosacea; therefore, use should be avoided in these cases.⁷

Diclofenac

Diclofenac 3% gel is a nonsteroidal anti-inflammatory drug that is believed to exert its effects through the inhibition of cyclooxygenase (COX), especially COX-2. The production of prostaglandins is thought to suppress the immune system, thereby allowing tumors to form.¹³ Without COX, prostaglandin production is reduced and the cascade is disrupted.¹³ Despite the more rigorous treatment regimen (twice-daily for 90 days), only mild to moderate local skin reactions are noted. Though rare, drug-induced hepatotoxicity reports have surfaced, consequently transaminases should be measured periodically in patients receiving long-term therapy.¹⁴

Imiquimod

Topical 5% imiquimod cream (Aldara®) was originally indicated as a treatment for genital and perianal warts; additional approved indications for treating AKs and superficial basal cell carcinomas followed. It is also used off label for treating Bowen's disease, invasive SCC, lentigo maligna, molluscum contagiosum, keloid scars, and others.¹⁵ Imiquimod acts as a toll-like receptor-7 agonist, which results in modification of the immune response and stimulation of apoptosis, thereby disrupting tumor proliferation.¹⁶ Stockfleth et al.¹⁷ demonstrated that 84% of treated AKs showed clinical clearance with one 12-week cycle of 5% imiquimod therapy. As with 5-FU, local irritant reactions are common. Coupled with its long duration of application (twice-weekly for 16 weeks), treatment adherence may be challenging with this agent. Administration to both the lesion and surrounding tissue targets both visible and subclinical AKs. Systemic effects, such as fatigue, flu-like symptoms, headaches, myalgias, and angioedema are rare.

Recently, regulatory approval was granted by Health Canada in December 2009 and by the US FDA in March 2010 to imiquimod 3.75% (Zyclara™) for the treatment of AKs on the face or balding scalp. Two identical placebo-controlled trials have evaluated the safety and efficacy of imiquimod 3.75%.^{18,19} In the trial by Swanson et al.,¹⁸ creams were applied daily to the entire face or balding scalp for two 2-week treatment cycles, separated by a 2-week interval without treatment. Patients applying imiquimod 3.75% achieved a median lesion reduction of 82%, while just over one-third demonstrated complete clearance. These efficacy data rival those achieved using imiquimod 5% twice-weekly for 16 weeks, with the advantage of significantly improved patient tolerance exhibited by the lower dosage. The therapy was found to be safe and did not result in any serious adverse events. Erythema was observed in most patients, with about 25% developing severe erythema. However, no patients withdrew from the study as a result of this; compliance rates were noted to be greater than 90%.^{18,19} Overall, the newly approved imiquimod 3.75% is a reasonable alternative to

imiquimod 5%, as it demonstrates comparable efficacy, allows for a much simplified, shorter dosing regimen, and seemingly yields less severe adverse effects. Additionally, imiquimod 3.75% is approved for the treatment of a larger surface area of up to 200cm², compared with 25cm² for the 5% formulation, and thus, is able to target more AKs.

Procedural Field Therapy

Procedural field therapies may be an appropriate option for patients who require minimal down time, are unlikely to adhere to a topical approach, have AKs resistant to topical therapy, or favor an optimal cosmetic result. Treatment options for procedural field therapy include photodynamic therapy, manual dermabrasion, laser resurfacing, cryopeeling, and chemical peels. Each of these techniques treats AKs by destroying the superficial layers of the skin through physical or chemical means.

Photodynamic Therapy

Photodynamic therapy (PDT) is a procedural field therapy that utilizes topical 5-aminolevulinic acid (ALA) or methyl aminolevulinate (Metvix®/Metvixia®) to target AKs. These molecules preferentially find their way into the hyperproliferating cells, which lack normal cell to cell adhesion junctions, and are converted intracellularly to protoporphyrin IX (PpIX).²⁰ This photosensitizer is then exposed to blue or red light, which corresponds to the peaks in the absorption spectrum of PpIX, resulting in a phototoxic reaction that destroys the abnormal cell.²⁰ PDT is effective for the treatment of multiple and diffuse AKs, and the cosmetic results are generally excellent. However, it is not ideal for treating thicker or deeper AKs²⁰ and is generally reserved for patients who exhibit an inadequate response to topical field therapy or cryosurgery. Patients may experience erythema, edema, and a burning sensation during the light therapy.

Conclusion

There is no widely accepted algorithm for the treatment of AKs. Often several different treatment regimens must be employed to manage AKs, especially with widespread or resistant cases. As always, the best way to manage AKs is prevention by avoiding exposure to significant or unnecessary UV radiation. Encouraging patients to wear broad-based sunscreens, wide-brimmed hat, sunglasses, and avoiding the sun during peak hours may prevent recurrence or limit the progression of AKs.

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Update on Drugs

Name/Company	Approval Dates/Comments
Imiquimod 3.75% cream <i>Zyclara</i> ™ Graceway Pharmaceuticals	The US FDA approved this topical immune response modifier in March 2010 for the treatment of clinically typical, visible, or palpable actinic keratoses. This new formulation offers a convenient 6-week dosing cycle and is indicated for application over larger areas of skin (as compared with imiquimod 5%), including the full face and balding scalp in adults.
Adapalene 0.1% lotion <i>Differin</i> ® Galderma Laboratories	The US FDA approved this novel lotion formulation of the retinoid adapalene in March 2010 for the treatment of acne vulgaris in patients 12 years of age and older. This new once-daily treatment has been designed to improve tolerable efficacy and spreads easily. It is available in an easy-to-use pump dispenser and is indicated for application on the face and other areas of the body that can be affected by acne.
Polidocanol injection <i>Asclera</i> ® BioForm Medical Inc./ Chemische Fabrik Kreussler & Co.	The US FDA approved this sclerotherapy agent in March 2010 to improve the appearance of varicose veins. This injection treatment is used to close spider veins (<1 millimeter in diameter) and reticular veins (1-3 millimeters in diameter). The agent acts by damaging the cell lining of blood vessels, causing the vessels to close, and then are subsequently replaced by other types of tissue.

DRUG NEWS

In April 2010, the US FDA issued warning letters to six US medical spas and a Brazilian company (Zipmed.net/Mesoone.com) for misbranding and allegedly making false or misleading website statements about certain drug products containing phosphatidylcholine and deoxycholate (PCDC). The therapeutic claims in question surround the elimination of fat when the agents are utilized in a procedure known as lipodissolve, which involves a series of micro-injections to the treatment site. The alleged mechanism of action is instigated when fat cells absorb the PCDC, causing inflammation and hardening. The hardened fat cells breakdown within a few weeks, resulting in their permanent removal. The procedure is also known by other names, such as mesotherapy, lipozap, lipotherapy, or injection lipolysis. According to the US FDA, these products are considered to be new drugs with unproven safety and efficacy, and may not be marketed unless the required regulatory authorization has been sought. More information is available at: <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm>.

IN MEMORIAM

We regret to announce the sudden passing of our
Managing Editor, **Penelope Gray-Allan**.

For more than 10 years, *Skin Therapy Letter*
benefited from Penny's enduring commitment and talents.

She will be greatly missed.