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Actinic Keratosis: A View from Down Under

Speaker: Dr. S. Shumack

Actinic keratosis (AK) is resulted from proliferation of neoplastic keratinocytes, caused by chronic exposure to ultraviolet radiation. AK should be treated owing to its malignant potential as they can evolve into squamous cell carcinoma. Other reasons for treatment include cosmetic improvement, contact bleeding and itchiness related to AK. The mainstay of therapy is cryotherapy with liquid nitrogen. Other treatment options include topical 40% trichloroacetic acid and 5-fluorouracil.

Imiquimod belongs to a new class of immune response modifiers. Imiquimod has been established as an effective treatment of genital warts. It has also been studied in treatment of AK. This compound stimulates locally both cellular and innate immunity and induces the immune system to recognise abnormal cells, leading to antitumour activity via the release of various cytokines. Imiquimod activates the immune cells by the Toll-like receptor 7 (TLR7)-MyD88-dependent pathway. The resulting antitumour activity is related to enhanced Th1 immune response and increased synthesis of interferon-α, interferon-γ and interleukin-12.

A number of studies have demonstrated the efficacy of imiquimod as a therapy for AK. The optimal protocol remains to be defined. Cyclical therapy is being used in the treatment of AK in Australia. According to this protocol, imiquimod is applied to a field of skin that includes AK, three times per week for three consecutive weeks. The patients is then reviewed four weeks later and the treatment cycle is repeated if there is less than 75% reduction in the number of AK. Another protocol is to apply imiquimod three times per week for three weeks and then two times per week from 4th to 12th weeks or stop earlier if AK has cleared. The total clearance rate quoted is 87.5% using this protocol.

The advantage of this therapy includes good tolerance to treatment with minimal adverse events. It causes little or no scarring compared to hypopigmented areas that can be associated with liquid nitrogen therapy and less pain or irritation sometimes associated with 5-fluorouracil therapy. Besides, subclinical AK within the treatment field becoming apparent during imiquimod therapy resolve similarly as the initially apparent AK. This may lead to a significantly longer remission period with imiquimod than those patients with only visible lesions treated with cryotherapy. The author also advised to avoid ears, eyelid and lips during imiquimod application.

Learning points:
A number of studies have demonstrated the efficacy of imiquimod as a therapy for actinic keratosis. The optimal protocol remains to be defined.

Improving the Treatment of Inflammatory Acne

Speaker: Dr. H. Gollnick

Consensus about the management of acne has not been reached among dermatologists. Unified therapeutic strategies of acne treatment are desirable so as to enhance patient compliance and effective use of healthcare resources. The primary pathology of acne is in the pilosebaceous units via the interplay of various pathologic factors. The principle of acne management is to deal with as many aspects of pathology as possible. All topical retinoids are effective in targeting the acne precursor lesions – microcomedones, leading to decrease in both comedones and subsequent inflammation. Antibiotics target bacteria in skin. Based on acne pathophysiology, the speaker advocated the use of topical retinoids, either alone or in combination with

antibiotics, as the initial therapy in most patients with mild to moderate acne.

The Toll-like receptors (TLRs) are implicated in the direct recognition of microbial pathogens by immune cells, triggering the release of proinflammatory cytokines such as TNFα and IL-1β. Activation of TLR-2 by components of *Propionibacterium acnes* might contribute to the inflammatory component of acne. Through this inflammatory signaling cascade, there is increased synthesis of matrix metalloproteinase (MMP). The degradation and repair of dermal matrix by MMPs upon repeated alteration of matrix will lead to acne scarring. Thus, the control of inflammation is important in reducing the acne scarring. The synthetic retinoid, adapalene, is shown to inhibit the expression of TLR-2 via the interaction with the retinoic acid receptors (RARs). The finding may account partly for the anti-inflammatory effect of this synthetic retinoid in acne.

Clinical trials have demonstrated greater reductions in both inflammatory lesions and comedones with the combined use of topical retinoids and antibiotics compared to topical or oral antibiotic monotherapy. Combination therapy cleared acne faster and had significantly greater reduction in both inflammatory and non-inflammatory lesion counts in randomised trials. The chronic use of antibiotics as the mainstay of treatment increases the risk of *P acnes* resistance in acne patients and selecting the pool of resistant organisms including *Staphylococcus aureus*. Dr James Leyden suggested that the duration of antibiotic in acne use should be minimised. Antibiotics should be stopped after clearing of acne lesions and the maintenance therapy should be switched to topical retinoids with or without topical benzoyl peroxide.

Females tend to experience acne beyond teenage. Similar therapeutic regime comprising topical and systemic treatments can be used in mild and moderate inflammatory acne as in males, except avoidance of tetracycline group during pregnancy. Hypersensitivity of sebaceous gland to androgens or overproduction of ovarian and adrenal androgen may play a role in pathogenesis of acne in females. Anti-androgens that block the action of androgens in the sebaceous ducts and sebocytes via competitive inhibition can be used in acne. Oral contraceptives are beneficial in women with mild acne who request contraception. The efficacy is due to estrogen component of oral contraceptives. The new generation of progentins in combined oral contraceptives have low androgenic potential. Other topical treatments may be combined with anti-androgen to hasten reduction of inflammatory lesions. Isotretinoin should be used in a more restricted manner in female because of its teratogenicity. Cyproterone acetate may be used in resistant inflammatory acne in adult women or in acne relapsing rapidly after treatment with isotretinoin.

Dr W. J. Cunliffe pointed out that the earliest clinical feature of acne is comedone and comedone formation is likely precede seborrhoea in pathogenesis. Previous study demonstrated that microcomedone was present in biopsies of normal looking skin in 29% of patients. Thus, it is important to apply topical therapy to all acne-prone sites and to use an effective topical therapy targeting comedone. The patient compliance to acne treatments is suboptimal and is related to inadequate advice by clinicians on the relatively slow response to treatment. Only 40% of patients were compliant to any form of acne treatments in a recent study by Dr Cunliffe's group. Better education of patients about acne and its therapy is essential. Topical treatment is used as monotherapy in mild disease and as combination therapy with oral antibiotics or hormonal therapy. More research needs to be done to confirm the usefulness of topical therapy following a course of oral isotretinoin. The choice of topical therapy depends on the type of acne. Topical retinoid should be the initial therapy. Topical antibiotics or benzyol peroxide should be added in inflammatory acne. Oral corticosteroid for a few days may be used in severe inflammatory acne and potent topical steroids may be applied to a developing large nodule to reduce scar formation.

Learning points:

Study demonstrated that microcomedone was present in biopsies of normal looking skin in 29% of acne patients. Thus, it is important to apply topical therapy to all acne-prone sites and to use an effective topical therapy targeting comedone.

Current Treatment for Leprosy

Speaker: Dr. D. Lockwood

The speaker emphasized that there was no large double blind control trial regarding the efficacy despite

that the WHO multi-drug regimes (rifampicin, dapsone, and clofazamine, MDR) have been used for many years. The speaker tried to analyze results of clinical trials to give an overview of the effectiveness of MDR treatment. The efficacy of other alternative regimes were also looked into.

Overall, the MDR is highly successful in that more than ten million patients had been treated. The regime includes rifampicin, which acts rapidly and renders patients non-infectious within 72 hours. The monthly-supervised dose is particularly cost-effective in remote areas of Africa and guarantee that patients have at least taking the supervised monthly dose.

In paucibacillary disease, the WHO MDR is effective in terms of clinical improvement and a low relapse rate after completion of treatment. However, in multi-bacillary disease, increase in the bacillary load increases the risk of relapse. If the bacteriological index (BI) is over 4, there is evidence that prolonging the MDR treatment beyond two years, until slit skin smear becoming negative will decrease the risk of relapse. But this may mean that treatment may have to be extended for longer than the two years recommended by WHO.

About the question of whether treatment could be shortened with more intensive treatment like 4 weeks' of rifampicin, minocycline and ofloxacin or 6 weeks' of rifampicin, ofloxacin, clofazamine and minocycline, there was an unacceptable increase in relapse rate for these shorter courses of therapy.

There is some progress in the use of single dose regime for slit skin smear negative single lesion disease. Single dose of rifampicin/ofloxacin/minocycline is almost as effective as standard WHO-MDR for paucibacillary disease. This regime is operatively attractive and may be suitable for some patients.

Learning points:

In leproxy patients with bacteriological index of over 4, there is evidence that prolonging the MDR treatment beyond two years, until slit skin smear becoming negative will decrease the risk of relapse.

Thalidomide Symposium: Thalidomide in Dermatology Workshop

An Overview of the Role of Thalidomide in the Management of Therapeutic-refractory Cutaneous Lupus Erythematosus (LE)

Speaker: Dr. V. Werth

Prior to 1993 relatively high dose (300-400 mg) of thalidomide was used to treat cutaneous LE. This had led to undesirable side effects. The speaker recommended using lower dose of around 100 mg/day for treatment of cutaneous LE.

Pooled up data showed that overall 60% of patients with cutaneous LE have complete response, 20% have partial response and 20% have no response to thalidomide. There is a fairly rapid response within two weeks with full clinical effects expected in 2-3 months' time. A lower maintenance dose of thalidomide (50 mg/day - 25 mg every three days) can then be given. Relapse can occur upon discontinuing even the very low dose of maintenance treatment. It is important to note that thalidomide has no effect on systemic LE.

There are reports of venous thrombosis in patients on thalidomide therapy. High risk patients include SLE with antiphospholipid antibody, myeloma and Behcet syndrome. The risk also increases in LE patients who are smokers and in women who are on contraceptive pills. Concomitant use of antimalarials decreases the risk of thrombosis. There is a risk of venous thrombosis when withdrawing antimalarial in patients not responding well to antimarials and putting them on thalidomide.

Safety Profile of Thalidomide

Speaker: Dr. J. Revuzs

Teratogenicity and neuropathy are the two serious side effects of thalidomide. Phocomelia is the most well known teratogenic effect. About 30% of pregnant women exposed will be affected. The speaker considered thalidomide less dangerous than isotreinoin in this regard as the former has a shorter

half-life and is now only indicated for patients with serious diseases. It is important that patients are fully informed of the side effects and have given consents to treatment. Women of childbearing age should be offered one and possibly two methods of contraception. It should not be given to woman for whom abortion is not an acceptable practice.

Neuropathy is the main factor limiting the use of thalidomide. Incidence of neuropathy is 25-55% depending on whether possible or dubious neuropathy is included in the analysis. The incidence is reported to be highest in the first year and is related to daily dosage of thalidomide. No neuropathy occurs if the dose is less than 25 mg/day. Using <50 mg as reference, the relative risk was 8.2 for 50-75 mg/day and 20.2 for >75 mg/day.

Thalidomide neuropathy is peripheral axonal and initially exclusively sensory. The patient may complain of distal parathesia with decreased tactile sensation on testing. Amplitude of sensory action potential would decrease while conduction velocity is normal. The first sign of neuropathy is electrical in 25% of patients. Regular nerve conduction study should be carried out in patients on thalidomide.

Other side effects include drowsiness, dizziness, asthenia and constipation. Endocrine disturbance, such as amenorrhoea and hypothyroidism, has been reported. Cutaneous side effects include erythematous maculopapular rash, facial oedema and severe drug rash.

Thalidomide and Emergent Conditions

Speaker: Dr. P. Wolkenstein

Toxic epidermal necrolysis (TEN) is a dermatological emergency with a mortality of around 30%. There is no specific therapy for this condition. Systemic corticosteroid has been shown either to have no therapeutic effect or even detrimental effect in TEN. The most important prognostic factor is the percentage of skin detachment and the aim of therapy is to stop the initial progression.

It is generally agreed that TNF is a pivotal cytokine leading to the extensive apotopsis in TEN. Thalidomide, being a potent inhibitor of TNF, had been studied in a double blind placebo-control trial for TEN. Thalidomide 400 mg or placebo was given for a five-day course in this randomized trial. This was however prematurely terminated due to increased mortality in the studied patients. In the thalidomide group 10 out of 12 patients died compared with only three deaths in 10 patients receiving placebo. There also appeared a paradoxical increase in the serum level of TNF in patients receiving thalidomide.

The speaker concluded that thalidomide is detrimental in TEN. Better understanding of the pathophysiology of TEN and the immunlomodulatory effect of thalidomide is needed for further study of any intervention in TEN.

Learning points:

The first sign of thalidomide neuropathy in electrical in 25% of patients. Regular nerve conduction study should be carried out in patients on thalidomide.