

The 5th Asian Dermatological Congress

reported by Dr. H.F. Ho and Dr. L.Y. Chong

Date: 14-17 October 1998
Venue: International Convention Centre, Beijing

Achilles Project - Overview and Preliminary Results

Speaker: Professor Rod Hay

In a satellite symposium on the new insights in epidemiology of foot pathology, Professor Hay from St. John's Institute of Dermatology in London gave an overview of this epidemiological survey of the prevalence of foot diseases. He also reported about the preliminary results of this project in Europe.

The Achilles Project consisted of a survey with a questionnaire and a study using mycological assessments. The former was conducted by both the general practitioners and the dermatologists, while the latter was done by the dermatologists. The aim was to assess the prevalence of foot diseases, since the epidemiological data were limited. The survey further assessed the prevalence of predisposing factors and the correlation between the quality of life and the foot and nail diseases.

During the one week study in Europe, 22,760 patients from Belgium, Netherlands, Luxembourg, Switzerland, Hungary, Britain and Poland were screened for foot diseases. Among the recruited population, 56% suffered from foot disorders. The most prevalent foot diseases were onychomycosis (26%), tinea pedis (24%), pes planus (12%), metatarsal corns (12%), hammer toes (8%), warts (6%) and gangrene (0.5%). Obesity, vascular disease and osteoarticular pathology appeared to be the most important predisposing factors in the affected population (respectively 25%, 24%, 25%). There was a high association between tinea pedis and onychomycosis, and both were highly prevalent in subjects with diabetes mellitus. Among the nail

disorders of the affected population, the following signs were most prevalent: discoloration (50%), hyperkeratosis (47%), and onycholysis (18%). The assessment of the quality of life revealed that 40% of the affected population presented with a discomfort in walking, 32% showed embarrassment for their condition, 26% felt pain and 18% were limited in their work.

This project has demonstrated a high frequency of foot diseases in the European population. However, the prevalence of onychomycosis seems higher than reported in other epidemiological studies and should therefore be further confirmed with mycological assessments.

N.B. The Achilles Project had also been conducted in Asia including China, Taiwan, Hong Kong, South Korea, Philippines, Singapore and Malaysia etc. The overall results were still undergone statistical analysis.

Learning points:

According to a recent epidemiologic survey in Europe, 56% of the recruited population is suffering from foot disorders. The most prevalent foot diseases are onychomycosis, tinea pedis, pes planus and metatarsal corns.

How to Detect Early Malignant Melanoma on the Sole

Speaker: Dr. Toshiaka Saida

The most prevalent site of malignant melanoma (MM) in non-white population is the sole of the foot. Early detection of MM on this site is important to improve the prognosis of this condition. In his presentation, Dr Saida presented to us his approach to detect early MM on the sole.

Dr Saida started his presentation by reviewing the histogenesis of MM on the sole. Since benign melanocytic nevus is commonly found on the sole, it is important to differentiate between MM and melanocytic nevus, and to clarify the relation between them. He provided evidence to support that the vast majority of MMs on the sole arise de novo as MM in situ. Careful histopathologic examination of MM in situ suggests that ordinary acquired melanocytic nevus is not related to histogenesis of MM.

Clinically MM in situ is observed as an acquired pigmented macule, variegated in color from tan to black, with asymmetrical irregular configuration, and the size is usually more than 9 mm at the time of diagnosis. In contrast, acquired melanocytic nevus is mostly 7 mm or less in maximum diameter, round or oval in shape, evenly pigmented.

Based on the data of size and clinical appearance of MM on the sole, the speaker and his co-workers proposed the following guideline for the early detection of plantar MM. Suspicious lesions will be excised for histology examination if the lesion's maximum diameter is more than 7 mm, or if the lesions present with features of asymmetry, irregularity and variegate in color. For lesions smaller than 7 mm maximum diameter and

without those suspicious features, only observation is necessary. Although this criterion overlooks small MM on the sole, it does not produce serious problems, because almost all lesions of MM on the sole are in curable thin stage if they are excised when they reach 7 mm.

Finally, Dr Saida shared his experience in using epiluminescent microscopy (ELM) for evaluating pigmented lesions on the sole. With a videomicroscope, they investigated ELM findings of 94 lesions, and found that there were substantial different patterns of pigmentation between acquired melanocytic nevus and MM. Macular portions of MM and MM in situ exhibited the characteristic "parallel ridge pattern", which represented selective pigmentation on the ridges of the surface skin marking. This "parallel ridge pattern" was not detected in acquired melanocytic nevi. Melanocytic nevi showed one of these 3 typical ELM patterns: parallel furrow, lattice-like, and fibrillar patterns. Histopathologic examination revealed that cristae profunda intermedia are mainly involved by the proliferation of atypical melanocytes in the early phase of MM, resulting in the ELM pattern showing preferential pigmentation on the surface ridges.

The speaker concluded that, their findings by using a videomicroscope support the usefulness of epiluminescent microscopy as a non-invasive method in detecting and diagnosing early MM on glabrous skin.

Learning points:

Take biopsy of pigmented macules on the sole to rule out malignant melanoma if maximum diameter is greater than 7 mm or lesions show irregularity, asymmetry, or variegate in color. Epiluminescent microscopy is a helpful, non-invasive tool if available.

Panniculitides: New Entity to Replace Old

Speaker: Dr. Martin M Black

Panniculitis is one of the most difficult and confusing areas in dermatopathology. Subcutaneous fat is vulnerable to trauma and noxious injury. Lack of lymphatic may delay the clearance of inflammatory mediators after damage and modify the inflammatory response. The clinical findings for many panniculitides are fairly similar, so a biopsy is often needed. Despite of that, biopsy does not always give the answer. Biopsies are often too small with inadequate fat. The response of adipose tissue is limited, and the histopathology findings depend on when the biopsy was taken in the time course of the disease.

In this lecture, Dr Black revised the four distinct histopathological patterns of panniculitis: septal panniculitis, lobular panniculitis, mixed panniculitis, panniculitis with vasculitis. He pointed out that although some degree of overlap may occur, this classification is helpful in resolving difficult clinical problems in the diagnosis and management of panniculitis. He also highlighted some relatively new panniculitis and reminded that syndromes like Weber-Christian disease and Rothman-Makai syndrome should be considered as obsolete.

1) **Septal panniculitis**- The classical disease is erythema nodosum (EN). The clinical spectrum of EN overlaps with EN-like lesions occurring in Sweet's syndrome and eosinophilic panniculitis.

Eosinophilic panniculitis has a distinctive pattern associated with a wide variety of processes. It may be localized or systemic. The association reported were: drug dependency, atopy, lymphoma, vasculitis, local injection, and Wells' syndrome. The panniculitis is characterized by prominent infiltration of fat lobules by eosinophils.

2) **Lobular panniculitis**- Dr Black emphasized that the clinical syndrome of Weber-Christian disease (relapsing nodular panniculitis) is almost certainly not a disease entity, but a syndrome resulting from a variety of causes that need to be identified. Newer entities include cytophagic panniculitis, alpha-1-antitrypsin deficiency panniculitis, and lipoatrophic panniculitis

which replaced the old entity Rothman-Makai syndrome.

Cytophagic panniculitis is characterized by patients presenting with recurrent subcutaneous nodules, fever, liver dysfunction, haemorrhagic diathesis and purpura. Patients often die of fatal haemorrhages, hepatic failure, pancytopenia, or an associated malignancy. This disease is associated with infections, lymphoproliferative disorders, allogeneic bone marrow transplantation and connective tissue diseases. Histological findings are lobular panniculitis with monocyte-macrophage infiltration, characterized by phagocytosis of erythrocytes, platelets, and lymphocytes by macrophages giving the appearance of "beanbag cells". Occasionally the panniculitis mainly shows a septal pattern.

Alpha-1-antitrypsin, synthesized in the liver, is the inhibitor of serine proteases circulating in the blood. The deficiency of alpha-1-antitrypsin results in unopposed proteolytic activity and the promotion of inflammatory reaction. Severe homozygous deficiency of this protease inhibitor results in a recurrent ulcerating panniculitis associated with emphysema, hepatitis, and acquired angioedema. Two patterns of panniculitis have been described: a lobular panniculitis with fat necrosis and a septal panniculitis with proteolysis of collagen and necrosis of the fibrous trabeculae. The presence of liquefactive necrosis of the dermis along with a similar pattern in the fibrous septa is thought to be characteristic.

Lipoatrophic panniculitis is a sub-type of localized lipoatrophies. Peters and Winkelmann first described it, although they used the term "atrophic connective tissue disease panniculitis". Patients presented with inflammatory nodules that expanded annularly leaving central lipoatrophy. Early biopsy demonstrated a lymphocytic panniculitis while latter biopsy showed atrophy of subcutaneous fat. Associated systemic disorders are diabetes mellitus, Hashimoto's thyroiditis, juvenile rheumatoid arthritis, and hepatitis.

3) **Mixed panniculitis**- In difficult cases of lobular or mixed panniculitis, it is necessary to polarize sections to exclude crystals (e.g. gout) or injected substances. Infective panniculitis is becoming more common in immunocompromised hosts. The lesions may be variable: subcutaneous nodules, EN-like lesions, erythematous plaques and ulcers. Bacterial organisms

are most commonly found, especially conventional and atypical mycobacteria, followed by fungi, Nocardia, and acanthamoeba. Epidermal and dermal changes are more frequent in infective panniculitis than in other panniculitis. Neutrophilic infiltrate is also a prominent feature. It is essential to sent specimen for special stain and culture.

4)Panniculitis with vasculitis- Vasculitis is a common component of panniculitis. Patients should be evaluated for size of vessel involvement, composition of infiltrate (neutrophils, eosinophils, lymphocytes, or granuloma), and systemic involvement such as infection, connective tissue disease or other systemic disease.

While the relation between nodular vasculitis (erythema induratum) and tuberculosis is still controversial, Dr Black commented that this entity could certainly be a true tuberculide. Tuberculosis can be identified if vigorously investigated.

In concluding his talk, the speaker summarized several points that were very useful in making a diagnosis in panniculitis. In order to establish the histological pattern of panniculitis, one should biopsy early active lesions instead of late-stage lesions. In difficult cases and appropriate circumstances, one should remember to examine specimen under polarized light and to perform special stain with culture for infection. The terms such as Weber-Christian disease and Roth-Makai syndrome should be avoided and newer disease entities should be considered. Finally, one must keep an open mind in difficult cases and be prepared to take new biopsy.

Learning points:

The keys to diagnosis of panniculitis are: biopsy active lesions, establish the histological pattern, polarize for foreign bodies and crystal, perform special stain and culture for infection.-

European Academy of Dermatology & Venereology - 7th Congress

reported by Dr. Y. M. Tang

Date: 7-10 October 1998
Venue: Acropolis, Nice, France

Clinical and Practical Aspects of Rosacea

Speakers: Dr. F. Powell, Dr. A. Rebora, Prof. G. Plewig, Dr. L E Millikan & Dr. B. Shroot

Epidemiological data, aetiologic and pathogenic hypothesis, triggering factors and clinical stages of rosacea (Dr. F. Powell & Dr. A. Rebora)

Rosacea is a common facial dermatosis but its aetiology remains a mystery. About 10% of workers in Sweden are affected, and it may be more common in certain parts of northern Europe. Pale skinned Celtic

racess seem to be particularly predisposed, indicating a genetic susceptibility, which is supported by a positive family history in 15% of patients.

Based on a US survey of more than 400 patients, a number of triggering/exacerbating factors have been identified below:

Factors	Percentage (%)
Sun exposure	61
Emotional	60
Hot weather	53
Alcohol	45
Spicy foods	43
Exercise	39
Wind	38
Hot baths	37
Cold weather	36
Hot drinks	36
Skin-care products	24

Four clinical stages can be identified which include flushing, erythema, papulo-pustules and phymas. One end of the spectrum is represented by flushing/telangiectasias in which there is vascular instability with a marked tendency to vasodilatation and the other end by phymatous disease in which there is thickening of the skin with sebaceous gland overgrowth and often little inflammatory change.

Flushing can be neurally mediated by circulating vasodilator agents. *Helicobacter pylori*, being a producer of nitric oxide, can be an effective potent vasodilator. Telangiectasia could be related to chronic sun-exposure which causes damage to connective tissue. Previous experiments discovered that dilated vessels can maintain their capacity to shrink and to dilate further. Their capacity to leak fluids will increase in parallel with the severity of the disease. Why some patients will move from functional stage to inflammatory stage is not clear. Cell-mediated and humoral hypersensitivity may play a possible role, as it was found that the undamaged connective tissue and demodex folliculorum could serve as antigenic determinants. Finally, recent studies on cytokines and growth factors suggested they could contribute to the development of phymas.

Where is the frontier between acne and rosacea? (Prof. G. Plewig)

Though acne and rosacea share similar features, they are separate diseases. A patient could have acne, rosacea or both. Instead of clarifying their distinctions, the term acne rosacea is confusing and should be discarded. Rosacea has episodic or persistent erythema, telangiectasia, follicular papules or papulopustules, but no comedones. There is usually prominent follicular opening but without scarring. Acne has comedones, papules or papulopustules and multiple forms of scars. Histologically, the two conditions share no common feature. Acne shows typical follicular keratinization (comedones), and commonly inflammatory changes. In rosacea there is no comedone formation, but there are oedema, telangiectasias, lymphectasias and connective tissue hyperplasia.

Current management of rosacea and prevention of relapses (Dr. L E Millikan)

The first step is to establish an accurate diagnosis since rosacea has its mimics such as seborrhoeic

dermatitis, adult acne, lupus erythematosus, photosensitive and contact dermatitis. The patient should be advised to avoid triggering factors such as spice, sun-exposure, hot foods and stress. Topical therapy is used initially for mild disease, while combined topical and systemic therapy is used for more advanced disease. Topical therapy includes metronidazole, sulfacetamide and clindamycin. They should be continued for four to six weeks. Antibiotics are the mainstay of systemic therapy. Tetracycline is most commonly used for its low cost and high efficacy. Some patients also improve with metronidazole, and some have a dramatic response to triple therapy for helicobacteria. Therapy should stabilise over the first three months of treatment. Since the disease severity fluctuates, treatment adjustment is needed. Granulomatous rosacea, a severe form of rosacea, mandates aggressive therapy. Systemic steroids could bring resolution in acute episode but should be tapered rapidly and followed with either dapsone or retinoids. Clinicians should aware that rosacea like reaction could occur after prolonged steroid therapy. Oedematous and sclerotic changes associated with various phymas are long-term complications that are difficult to treat. Laser resurfacing is now regarded as an effective treatment for rhinophymas.

Rosacea: future trends (Dr. B. Shroot)

The pathogenetic factors for rosacea are speculative, but a genetic component appears to be involved. The fact that drugs used currently to manage rosacea act through unknown mechanisms stresses the need for further research. Dermal endothelial cells should be one focus of research attention, because the onset of symptoms and signs are inflammatory in nature. In this context, a better understanding of how current and emerging therapies act on the endothelin and nitric oxide signaling pathways will be helpful. These may provide a good hint on how to improve the established drugs and help to discover more effective agents. Preliminary results with topical nitric oxide synthase inhibitors appear encouraging.

Learning points:

Oedematous and sclerotic changes associated with rhinophymas in rosacea are long-term complications that are difficult to treat. Laser resurfacing is now regarded as an effective treatment.

Chemical Peeling

Speaker: Dr. H. Ghersetich

Chemical peeling (CP) consists in the application on the skin of exfoliating agents resulting in destruction of part of the epidermis and/or dermis with subsequent regeneration of new tissue. This technique produces a controlled wound determining cutaneous renewal with reduction or disappearance of actinic keratoses, pigmentary dyschromia, wrinkles and superficial depressed scars.

CP induces a modification of the skin according to the wound depth through the following mechanism:

1. Stimulation of epidermal growth following the removal of the stratum corneum.
2. Destruction of the damaged cutaneous layers leading to regeneration of "normal" tissue. This is mandatory in some cutaneous alterations such as actinic keratoses or pigmentary dyschromias.
3. Induction of an inflammatory reaction in deeper skin layers. The release of mediators of inflammation may induce new collagen synthesis and extracellular matrix deposition in the dermis.

Glycolic acid peeling

Formula

One formula used by the speaker is a 70% glycolic acid solution (Glypure). The formulation is photostable but evaporates easily. Therefore, it should be kept in well-closed bottle. The stability can last for more than two years.

Skin priming

A two-week preparation with a cream containing retinoic acid and/or alpha hydroxy acids together with a cutaneous bleaching agent according to the skin type and the specific skin disorder of the patient are used.

Degreasing

Alcohol or acetone is used. This allows a homogeneous and deeper penetration of the peel.

Application

The application can be performed with a special brush, a Q-tip or a piece of gauze. Once applied, the operator should observe for erythema or frosting that represents epidermolysis. Neutralization should then be done.

Neutralization

An alkaline solution (e.g sodium bicarbonate solution) is used in the neutralization process. This allows the perception of effervescence caused by the release of carbon dioxide which will terminate after completion of neutralization.

Postpeel care

No alpha hydroxy acid should be used for 2-3 days. Topical non-halogenated steroid can be used for erythema for 2-3 days. Antibiotic cream can be used for a week if abrasion occurs.

Resorcinol peeling

Formula

Resorcinol is related to phenol. It can break the weak bonds of keratin to hydrogen. When used in creamy formulations, its concentrations vary from 10-50%. This type of peeling is easy to handle and side effects are low (mainly transient hyperpigmentation). This peel is useful in patients with superficial acne scars and melasma.

Skin priming

One month of combination of 4% hydroquinone, 1% hydrocortisone and 0.05% retinoic acid is used for melasma patients.

Application

The cream is applied with a spatula on the area to be treated and kept for a period of 60 to 120 minutes. A reaction similar to first degree burn with further exfoliation that generally lasts from one week to ten days. No specific neutralization is needed as that for glycolic peel.

Postpeel care

Antibiotic and non-halogenated steroid creams for one week and patient is advised to protect against UV radiation for at least one month.

Trichloroacetic acid (TCA) peeling

Formula

This is a very efficient peeling for elastosis, slight wrinkles, actinic keratosis and scars. Pigmentary changes (lentigo simplex, melasma or post-inflammatory hyperpigmentation) give variable results,

and possibility of worsening should be considered. If used at concentrations below 40%, the risk of scarring is low. The deep and perioral wrinkles respond only moderately to this treatment.

Crystal TCA at 20-50%, in water solution is not photosensitive and is stable for at least 23 weeks.

Skin priming

Priming is important to allow a more uniform penetration of the peel, to reduce the re-epithelialization phase, and to minimize the risk of post-inflammatory pigmentation. Retinoic acid 0.1% is used daily for at least 15 days. Alpha hydroxy acids, hydroquinone or kojic acid may be used together with SPF 15 (or more) sunscreen.

Degreasing

Degreasing agents like alcohol or acetone solution is used as for other peelings.

Application

TCA may be applied with a Q-tip or a gauze. The first application is done on the area to be treated, allowing the substances to penetrate for a few seconds and then, a further application and so on until frosting appears (whitening due to the coagulation of proteins of the epidermis), indicating that the acid has penetrated down to the papillary dermis. Water is then sprinkled

onto the treated area. TCA treatment takes about 15 minutes and the application is painful to the patient. Therefore topical anaesthesia, sedatives or analgesics may be required in some cases. Even the patients has a limited area to be treated, a light peeling all over the face is recommendable in order to avoid dyschromias. Since the depth of the peeling increases with more coats, the application should be limited to one or two coats if higher concentrations (e.g 50%) of TCA are used.

Post-peeling care

Antibiotic creams followed by an hydrogel dressing are used. Mild itching and exfoliation may occur but patients should refrain from removing the scales to avoid post-inflammatory hyperpigmentation. In the following two to three weeks, the skin usually maintain a pink colour, and a non-halogenated corticosteroid cream can quicken the recovery to normal skin colour. Ultra-violet light avoidance is required for four to five months.

Learning points:

Chemical peeling destroys damaged cutaneous layers, stimulates epidermal growth, and induces new collagen synthesis & extracellular matrix deposition, leading to a modification of skin according to the depth of wound.

Management of Male Androgenetic Alopecia

Speakers: Dr. W.F. Bergfeld, Dr. D. A. Whiting, Dr. D. Van Neste & Dr. V. H. Price

Roles of hormones (Dr. W.F. Bergfeld)

Hair growth involves complex interactions of gene, signaling factors, cell-to-cell interactions, complex proteins and hormones. The hair growth cycle is the result of many controlled and programmed events. The primary follicle stem cells are within the bulge area. The secondary site is the anagen bulb that composes follicular epithelium and the dermal papillae. The dermal papillae and sebaceous gland contain androgen receptors, the number of which varies according to genetic factors, sex and sites. Androgens are important modulators of hair growth. In male, the conversion of testosterone (T) to dihydrotestosterone (DHT) produces seborrhoea, alopecia, hirsutism and acne. The three

major enzymes involved in the conversion are: 5 α -reductase, aromatase and 3, β -hydroxysteroid dehydrogenase isomerase. In balding scalps, there are increased androgen receptors, and increased 5 α -reductase as compared to non-balding sites. DHT inhibits adenylyl cyclase activity which interferes with cAMP, affecting the anagen cycle. Aromatase appears to protect against scalp baldness. Androgenetic alopecia (AGA), an autosomal disorder with an onset at puberty, is associated with increased circulating dehydroepiandrosterone and signs of sexual development and sexual hair. The mechanisms driving AGA appear to be due to both the increased circulation and metabolism of androgens at the hair follicles, especially the dermal papillae and external root sheaths.

Role of hair biopsies (Dr. D. A . Whiting)

Scalp biopsies can be standardized using a 4 mm disposable biopsy punch. The biopsy needs to be directed deep into the subcutaneous tissue and parallel to any existing hair shafts. This biopsy should be deep enough to include the subcutaneous fat so that terminal hair roots can be examined. Both horizontal and vertical biopsies should be examined for the best information.

Light microscopy on vertical section can detect terminal hairs, streamers, and vellus hairs. Additionally, any inflammation, fibrosis, epidermal abnormalities and other pathologic changes can also be detected. Follicular units, terminal (at different stages) and vellus hairs can be counted accurately in the horizontal sections. In addition, pathological changes can also be detected. A follicular unit at mid dermal level near sebaceous ducts is roughly hexagonal in shape and 1 mm² in size. Normally, each follicular unit houses two to four terminal hair follicles, sebaceous lobules and ducts, arrector pili muscles and 0 to 2 vellus hair follicles. The total hair counts can be made, and the anagen and telogen percentages, as well as the terminal to vellus hair ratio can also be calculated. In androgenetic alopecia, the terminal to vellus hair ratio is often reduced to less than 4:1. This indicates increased follicular miniaturization.

Role of phototrichogram (Dr. D. Van Neste)

Quantification of the severity of alopecia can be achieved by counting the number of visible hair per unit on human scalp. This can be done by performing phototrichogram which consists of comparing two shots taken at an appropriate time interval (usually 2-3 days) after adequate scalp preparation. This method adds more dynamic dimensions to the static hair number, i.e. growth measurement, linear hair growth rate and the anagen percentage. The latter is a determinant for the measurement of the cosmetic significance of scalp hair.

Finasteride: review of clinical data (Dr. V. H. Price)

Increased 5 α reduction of testosterone to DHT is implicated in the pathogenesis of androgenetic alopecia. The central role of DHT was clarified by studies in men with a genetic deficiency of type II 5 α -reductase who

do not develop male pattern hair loss (MPHL). Treatment with finasteride, a type II 5 α -reductase inhibitor, lowers circulating and scalp DHT. Studies have shown that adult male patients given oral finasteride 1 mg daily for 12 months had increased scalp hairs in all parameters evaluated, including scalp hair counts, investigator and patient self-assessments, and global photography.

In one study involving 1,553 men with vertex baldness, 1,215 selected to continue for a 12-month extension. At the end of two years, standardized global photography showed that 66% of the men receiving finasteride had increased hair growth. In contrast, only 7% of placebo treated men showed increased hair growth.

Safety of finasteride at 1 mg/day orally was evaluated in over 3,200 men participating in MPHL studies and was found to be very safe. In about 1% of patients, there was decreased libido, erectile dysfunction, or decreased ejaculation. This was similar to the placebo group. These side effects resolved when therapy was discontinued and in 58% of men who continued treatment with finasteride. Laboratory tests showed a significant reduction of DHT in scalp and plasma but only slight elevation of testosterone in the plasma. However, the serum prostatic specific antigen (PSA) was also reduced, therefore such reduction should be taken into account when interpreting the PSA level in the context of prostatic diseases. Finasteride should not be given to women who are or may be pregnant because of its potential adverse effect on male foetal sex development.

It appears that male patients with definite scalp thinning and lots of miniaturized hairs are good candidate for the treatment, whilst it is not effective for post-menopausal women.

Learning points:

For androgenetic alopecia, male patients with definite scalp thinning and lots of miniaturized hairs appear to be good candidates for oral finasteride treatment. Only around 1% of patients have decreased libido, erectile dysfunction or decreased ejaculation.

Actions and Role of Imiquimod on the Management of Genital Warts

reported by Dr. C. K. Ho

Date:	9 October 1998
Venue:	Lecture Hall, Sai Ying Pun JCC
Speaker:	Dr. Kenneth Trofatter
Organizer:	Social Hygiene Service, DH

Genital human papilloma virus (HPV) infection is one of the commonest sexually transmitted diseases. However, treatment for this infection remains unsatisfactory as current therapies are slow in action, with a high recurrence rate and the added inconvenience of requiring regular clinic attendance. In addition, although most HPV infections are of low carcinogenic potential, some serotypes (particularly 16 and 18) are associated with an increased risk of malignancy.

Cell-mediated immunity (CMI) is important for the control of HPV infection, as can be seen from the increased severity and reduced response to treatment of genital warts in HIV-infected patients. Reduced CMI results in a higher risk of malignant transformation due to HPV infection.

Imiquimod (Aldara) is an immunomodulatory agent which has no direct activity on HPV infection. It acts by enhancing CMI through induction of cytokine production from monocytes and macrophages. This occurs through activation of protein and tyrosine kinase via interaction with cell surface receptors. Alpha-interferon (IFN- α) is the principle cytokine induced by imiquimod. Other cytokines induced are tumour necrosis factor (TNF) and interleukins (IL)-1, 6, and 8. This results in stimulation of cytotoxic T-cells, neutrophils and natural killer cells with enhanced antiviral activity. An intact immune system is therefore required for an adequate response.

In a double-blind study comparing 5% imiquimod, 1% imiquimod and vehicle control, 311 patients with perianal/genital warts were treated three times per week for a maximum of 16 weeks. The cream was washed

off after eight hours. The clearance rate of vehicle and 1% imiquimod cream were similarly low (20% for females; 5% for males). The clearance rate for 5% imiquimod cream was 72% for females and 33% for males. This was significantly more effective than vehicle or 1% imiquimod cream. Partial clearance of warts was greater for females than for males. The mean time to clearance for females was eight weeks and for males, 12 weeks. In addition, patients who achieved total clearance tended to remain clear. Those who relapsed tended to do so in milder forms, even in cases with initially extensive disease. There was no significant difference between the recurrence rates of 5% imiquimod cream and vehicle (13% vs 10% respectively).

The main side effect was erythema, affecting two-thirds of patients. Other side-effects included erosion, excoriation, induration, ulceration and oedema. Severe skin reactions occurred in 6% of patients. Itching and burning were the most frequent local reactions. These subsided after stopping treatment, after which, the treatment was able to be continued. Imiquimod was shown to be less irritating when compared to a skin-care lotion.

Animal studies have shown no evidence of teratogenicity, cytotoxicity, or carcinogenicity. However, as data on use in pregnancy is scanty at present, it is not recommended for use in pregnancy. Studies have shown that there is minimal systemic absorption through intact skin with 5% topical imiquimod.

During the discussion, treatment of HIV patients with imiquimod was discussed. As an intact immune system is required, response to imiquimod may be suboptimal in patients with advanced disease. However, with advances in treatment regimens for HIV, the prospects of preserving the immune system has improved. Imiquimod may therefore be a suitable option for these patients in the future. There is also the concern of imiquimod induced idiosyncratic reactions in HIV patients as well as in transplant patients. Questions were

also raised concerning the relative efficacy of imiquimod compared with conventional therapies. There is no formal data on this issue to date.

In conclusion, Imiquimod represents a novel alternative to conventional therapies. Studies to date have shown that it is well tolerated with promising results. It has the additional advantage of being licensed for home-use for genital and perianal warts. It is not licensed for mucosal warts at present.

Learning points:

Imiquimod is an immunomodulatory agent acts by augmenting the cell-mediated immunity and has no direct action on HPV infection. An intact immune system is therefore required for an adequate response.