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CONTINUING MEDICAL EDUCATION

TREATMENT OF PSORIASIS

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Psoriasis is a world-wide disease with a prevalence of 0.1-2.8%, [1-5] rare before 3 years age with a peak incidence between 14-40 years. Both sexes and almost all ethnic groups are affected. The course is chronic, attended with the development of physical disfigurement, disability, psychological and economic stress. Exact etiology is unknown, probably it is multi-factorial. Van Scott and Ekel[6] in 1963 reported 27 times faster rate of mitosis in psoriasis compared to normal epidermis. The cell cycle is reduced from 311 to 36 hours, the proliferative basal cells actually concerned in division are nearly doubled.[7,8] In younger patients genetic predisposition is thought to be causally related. Generally, the disease appears following additional assaults like infection, trauma, drugs like lithium, chloroquin and beta-blockers, low humidity, stress, hormonal variations and smoking. The genetic susceptibility is variable, perhaps polygenic and is documented by a significant increase in the frequency of HLA antigens B^{13}, B^{17}, B^{16} and CT^{1} in patients with psoriasis.[9,10] Voorhees et al 1973[11] found low levels of cyclic AMP and high levels of cyclic GMP in psoriatic epidermis and proposed that enhanced epidermal cell proliferation is the result of altered ratio of the two enzymes. Abnormal accumulation of neutrophils (PMN) is observed in the dermis during relapse, while the epidermis remains normal. As the lesions resolve, the clearing of inflammatory reaction is seen.[12] The directed chemotaxis of neutrophils was significantly increased in all the patients when compared with controls in a study by Datta et al.[13] The recognised variants of psoriasis are, vulgaris, guttate, pustular, erythrodermic and psoriatic arthropathy. The erythrodermic, arthropathic and pustular forms are serious syndromes and require intensive management. The course and prognosis of psoriasis are unpredictable, only 40% patients have prolonged remission on long follow up. The severity may very from minimal cosmetic problem to a life-threatening emergency, but it is rarely fatal.[14]

The treatment modalities selected should not be unpleasant or dangerous than the disease itself and the complexity should be appropriate to the patients's intelligence, occupation, social and economic background. Since the basic abnormality is increased epidermal cell proliferation, most treatments are aimed at slowing down the rapid proliferation of epidermal cells. Though no cure is yet available in the ordinary sense of the word, topical and systemic therapeutic modalities administered singly or in combination are fairly effective in maintaining the control of the disease.[15,16] The available forms of treatment can be considered under five main headings:

1. Removal of the triggering factors.
2. General measures like reassurance, rest, holiday and explanation.
3. Topical therapy with tar, dithranol, keratolytics, emollients and corticosteroids.

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4. Systemic therapy with corticosteroids, methotrexate, PUVA, etretinate, hydroxyurea and others.
5. Phototherapy with (UVB).
6. Other treatment modalities.

While making selection for the treatment modality for a particular patient, decision has to be made about need for maintenance treatment or the possibility of achieving a prolonged remission with a short sharp course. There are no clear rules, each patient has to be evaluated on his or her own merits.

General Measures

Reassurance that the disease is not contagious or malignant is often fruitful. Explanation that spontaneous resolution occurs and treatment can improve the disease, although recurrence is possible, helps a lot. Fear for the future of children may be allayed and the patients enlightened with the available knowledge about genetic predisposition. Evaluation of the daily routine of the patient and suggestions regarding reducing stresses and a holiday in sunshine (climatotherapy) often help both the skin and the psyche. Diet is unimportant, elimination of obvious infection or correction of metabolic disorders is often helpful. In all forms of unstable, pustular and erythrodermic psoriasis, rest in bed preferably hospitalisation is imperative.

Topical Therapy

The choice of topical agents depends on the site, size and thickness of the psoriatic plaques. The efforts to clean up messy local preparations have not been completely successful. The drawback exists equally with the time-old tar and the newer elegant and expensive preparations.

Tar Therapy: Crude coal tar contains innumerable hydrocarbon compounds. The therapeutic effect is brought about by enzyme inhibition and antimitotic action, though the exact mode of action of this traditional therapy is not entirely known. It is the basis of the widely used Goeckerman regimen[17,18] which consists of application of crude coal tar (2 to 5%) to the skin for 24 hours, after 24 hours most of the tar is removed by the use of an oil followed by exposure to ultraviolet light and then the patient is given a cleansing bath with ordinary bath soap and the tar is reapplied. This regimen clears widespread psoriasis within 3-4 weeks and may effect a remission for weeks to months. Tar can be incorporated in soaps, shampoos or baths and can be dispensed in the form of creams, ointments, pastes, lotions and as coal tar solution.

Tar should be the first choice for majority of the patients with mild, guttate, or scalp lesions, and psoriasis in children. DesGroseilliers et al[19] reported clearance in 86% of patients with ambulatory Goeckerman treatment given 5 days a week for one month. Remission lasted for approximately 5.1 months. Many controlled studies substantiating the effectiveness and safety of tars, alone[20-23] and in combination with UV light are available.[24-26] Tar is extremely safe, allergic contact sensitization even with repeated applications is rare, primary irritation is unusual except when used on very inflamed lesions. The use of tar was not found to be associated with the risk of development of cutaneous malignancy in the treatment of psoriasis in a review of 55 years experience at the Mayo Clinic in Rochester, Minnesota.[27-29]

Dithranol (Anthralin): Dithranol is a synthetic compound that has been used effectively for the treatment of psoriasis since 1916,[30] and formed the basis of the popular Ingram regimen.[31,32] The exact mode of action is unknown, it probably involves inhibition of DNA replication and repair.[33] The interference seems to be specific for mitochondrial DNA.[34,35]

If tar fails, dithranol may be used, as it is more effective, faster in action and can be used for both out-patients and in-patients. Concentrations of 0.05% to 2% clear most psoriatic lesions within 3 weeks. As first-line topical therapy dithranol is indicated when the lesions are large and few. In the standard Ingram regimen,[31] dithranol paste is applied in a low concentration (0.1 to 0.5%), precisely over the lesions, usually overnight. Cotton stockinette dressings are worn while the paste is on the skin overnight. After ultraviolet exposure the following day, the preparation is thoroughly rubbed off by a tar bath before the treatment is repeated. Care should be taken to avoid contacting the eyes with dithranol.

Numerous variations on the use of dithranol have evolved in different regions of the world[36] involving:

1. Modification of dithranol vehicles.[37,38]
2. Modification of dithranol concentrations.[39-41]
3. Modification of length of application.[42,43]
4. Introduction of new derivatives for reducing the irritation and staining.[44]
5. Combination of dithranol with other regimens for getting additive clinical effect.[45-47]

Kaur et al[50] tried graded concentrations of the compound dithranol ointment, in 107 patients having stable plaque psoriasis, with 0.05% concentration which was gradually increased, irrespective of the response, to the maximum tolerable concentration. Majority of patients required a concentration of 0.25% for clearing, though a few required 0.5% concentration. There was complete clearing of the lesions in 54% patients, 22% showed 75% clearance in an average period of 10.5 weeks. Mild local side effects including, irritation of the surrounding normal skin, temporary staining of finger tips, nails, clothes and linen occurred.

Short contact therapy with dithranol was first suggested in 1980 by Schaffer et al.[42] In this treatment regimen, a higher strength of dithranol ointment.[42] paste [51] or cream[52] is applied topically for a limited period to minimise the side effects without impeding the therapeutic efficacy. This regimen is the most convenient, clinically effective and readily acceptable mode of application for use at home.

Short contact dithranol therapy is being tried at the psoriasis clinic of our Institute using commercially available derobin ointment (half diluted with petrolatum, and full strength (1.15%), dithrocream (0.5% and 1% obtained with the courtesy of Mr. M. Yarrow from UK), dithranol ointment (1.5% and 3%, dispensed from pure dithranol powder obtained from Glaxo Labs (I) Ltd Thane). In the derobin ointment group, complete clearance occurred after a mean period of 29.75 days with diluted (0.5%) and full strength (1.15%). No statistically significant difference was found in the time taken for clearance with different concentrations. However, the improvement started earlier with full strength derobin ointment. No side effects other than staining of normal skin were observed. The limited application time is convenient for home and better patient compliance.

The irritation and staining of skin are transient and disappear within a week or two.[38] Dithranol should not be applied to the lesions on head, neck, body folds and genitalia. Dithranol is the first-line treatment for suitable cases in many countries because of its high degree of safety and efficacy.[53-56]

Corticosteroids: Topical corticosteroid creams and ointments can lead to rapid and good improvement of psoriasis, but the improvement is short lasting and is often followed by relapse, which is earlier than in the case of tar and dithranol. The most potent topical corticosteroid preparations are clobetasol propionate and fluocinolone acetonide (0.2%), the least potent are hydrocortisone, dexamethasone and betamethasone.

The weak steroid preparations should be used for areas like scalp, face, ears, neck, flexures and genitalia where dithranol is often unmanagable and tar unpleasant. The strong steroid preparations may be used for short periods for the treatment of resistant psoriasis of hands and feet. The effect of steroid can be enhanced by polythene occlusion.[57] Prolonged use of potent steroids can cause cutaneous atrophy, telangiectasia and striae.

Phototherapy: In a study carried out on 5600 patients, 80% benefited from natural sunlight.[58] Exposure to artificial UV irradiation is also helpful. It is an important adjunct to many topical and systemic antipsoriatic therapies.[59-62] The eyes should be protected from the injurious rays. The prevalence of premalignant and malignant skin lesions among extensively UVB-treated psoriatic patients compared with control group of healthy patients,[49] indicated that psoriasis patients were no more at risk in this respect than the control group.

Bland Preparations: In an acute or unstable psoriasis, injudicious treatment with irritant and potent preparations can precipitate erythroderma. Bland preparations such as calamine lotion with or without oil, soft white paraffin etc may be used.

Systemic Therapy

There is no entirely safe, long-term systemic treatment for psoriasis. Systemic therapy must be reserved for truly disabling or life-threatening psoriasis resistant to conventional therapy.

Corticosteroids: In the routine management of psoriasis, corticosteroids have no place. After initial improvement, the disease always relapses on withdrawal of corticoids or reduction of the dose. Erythrodermic or generalised pustular phases of psoriasis may be precipitated. Corticosteroids have a role in the management of persistent, uncontrollable, erythrodermic psoriasis causing metabolic complications, and in fulminating generalised pustular psoriasis of the von Zumbusch type, if administration of methotrexate is contra-indicated. Associated psoriatic arthropathy is not per se an indication, but steroids may occasionally be needed for the control of acute polyarthritis which is threatening severe irreversible joint damage.

Methotrexate: The antimetabolite methotrexate (MTX) has been used for the treatment of intractable and crippling psoriasis for the past over 20 years.[63-65] According to the guidelines of Psoriasis Task Force of National Programme for Dermatology,[66-68] the indications for methotrexate therapy are:

1. Psoriatic erythroderma,
2. Psoriatic arthropathy,
3. Acute generalised pustular psoriasis,
4. Extensive uncontrollable disease,
5. Psoriasis in areas of body preventing gainful employment.

Methotrexate has been used when topical therapy failed or when the disease caused severe disability including serious emotional problems. The near absolute contra-indications for methotrexate therapy are, significant hepatic and renal damage, pregnancy, fibrosis or cirrhosis of liver, severe anaemia, leucopenia or thrombocytopenia, active peptic ulcer, excessive alcohol intake, active infectious diseases and a unreliable patient. A relative contra-indication in both sexes is the fertile period of life.

Before starting methotrexate, individual patient assessment should be made. The pre-methotrexate evaluation should include complete haematological profile, renal and liver function tests including serum enzymes, liver biopsy and x-ray of chest. Continuing evaluation should be undertaken weekly for haematological parameters (Hb, platelets and

leucocytes) and later at 2 to 3 month intervals, renal and liver functions are repeated at 3-6 month intervals and yearly x-ray of the chest. The liver biopsy is assessed yearly[69] or when the cumulative dose of methotrexate exceeds 1.5 gm.

Methotrexate acts by inhibiting the enzyme dihydrofolate reductase and blocking the synthesis of thymidylate, one of the four precursors of DNA, thereby arresting cell division. The drug is given orally or parenterally in a dose of 0.2-0.4 mg/kg body weight. Out of the three recommended dosage schedules, the weekly single oral dosage schedule[66-68] is the safest and most accepted. A divided intermittent oral schedule given 12 hourly over a 36 hour period each week[65, 70] is most effective. The indications for stopping methotrexate are following:

1. WBC less than 4000/mm^3.
2. Fall in haematocrit of 10%.
3. Thrombocytopenia.
4. Persistent abnormal liver function tests.
5. No response after 8 weeks.
6. Diarrhoea, ulcerative stomatitis.
7. Liver biopsy changes. The drug should be avoided in grade III and IV damage, administration can be continued in grade I and II changes when the damage is reversible.

The adverse reactions reported are malaise, chills, fever, dizziness, susceptibility to infection, skin rashes, urticaria, alopecia and ecchymosis etc. Bone marrow depression may occur. Gastro-intestinal toxicity may be manifested by gingivitis, vomiting, diarrhoea or ulcerative stomatitis.[69,70] Severe hepato and nephrotoxicity can occur. Oligospermia, menstrual disturbance and various types of psychosis and depression may occur. Pregnancy should be avoided during therapy and for 3 months after stopping the treatment. The risk factors for increasing liver damage are obesity, advanced age, excessive alcohol intake and diabetes mellitus.

In a study by Kaur et al,[71] majority of the patients experienced 75% clearance. Follow up of 3 years did not reveal side effects necessitating discontinuation of MTX. Males tolerated the drug better. Topical therapy may be combined to keep the dose of MTX low. Methotrexate combined with PUVA[72] or retinoids[73] resulted in more rapid clearance, compared to either drug alone. A retrospective study on the use of methotrexate in psoriatic arthritis has been published by Kragballe et al.[74] Methotrexate per se has not much effect on psoriatic arthropathy but with the over all improvement in the skin condition the joint problem also tends to improve.

Although MTX is a safe and effective drug for the treatment of refractory psoriasis, the patients should be constantly supervised and the therapy discontinued if toxicity develops.

Other antimitotic drugs such as azathioprine[75] and hydroxyurea[76] have been used in psoriasis but they are less effective than methotrexate and tend to damage the bone marrow more than the liver.

PUVA: The PUVA therapy, the photosensitizing drug 8-methoxypsoralen is given orally in a dose of 0.6 mg/kg weight, and 2 to 3 hours later the patient is exposed to long wave ultraviolet light (UVA 320-400 nm). An average of 25 treatments given 2 or 3 times weekly are required for 80% clearing. PUVA is well established as an effective treatment for psoriasis.[77] The mechanism of action is inhibition of DNA synthesis and cell division. Indications for PUVA are:

1. Severely incapacitating psoriasis not controlled by conventional treatment.
2. Psoriasis not controlled or patients intolerant to methotrexate or have developed hepatic damage while taking it.
3. Moderately severe psoriasis with liver damage which is a contra-indication to methotrexate therapy.

Contra-indications: PUVA should not be used in children, pregnant women, patients with known light sensitivity and mild cases normally responsive to other measures.

Erythema and blistering are acute side effects due to phototoxicity, but are dose related and thus can be controlled. Nausea,[78] pruritus, headache and dizziness may accompany treatment. Of great concern are the potential long-term side effects such as cataract formation,[79] carcinogenecity[80] and immune dysfunction,[81] Farber et al[61,62] caution that the risks of chronic toxicity from PUVA underscore the need for proper selection of the patients, the administration of PUVA for a limited period and the use of adjunctive agents either in combination or sequentially to minimise the total PUVA dosage.[82,83] The main reservation about the widespread use of PUVA lies in the potential long-term hazards of accelerated aging and carcinogenesis.

Razoxane: Razoxane is 1.2 bis-(3.5 dioxopiperizin-2-yl) propane derived from EDTA. It is an oral antimitotic agent, which has been proved effective in intractable psoriasis[84] where other modes of therapy have failed. It has advantage over methotrexate as it does not produce hepatotoxicity.

Indications: (1) Pre-existing liver disease precluding treatment with methotrexate. (2) Hepatotoxicity developing during treatment with methotrexate. (3) Patients not tolerating methotrexate due to excessive nausea and vomiting.

Exact mode of action is not known, it arrests the cell cycle in the late "G_2" or early M phases. Probably the drug is better absorbed when given in divided oral doses than as a single large daily dose. A dose of 125 mg three times a day for 2 days in a week is given initially for 4 to 8 weeks and repeated after 7-14 days.

Side effects are mild like, neutropenia which is dose-dependent and reversible, slight reduction of haemoglobin concentration, diffuse alopecia, nausea, lethargy, headache and diarrhoea. Though the drug is free from hepatotoxicity, further evaluation is essential.

Retinoids: Oral etretinate, an analogue of vitamin A acid (retinoic acid) has been shown to be effective in psoriasis when used alone or in combination with other agents.[85,86]

The indications are, (1) Pustular types of psoriasis, (2) Erythrodermic psoriasis, and (3) Extensive and refractory psoriasis.

Since the drug is teratogenic, it should not be used in women of child-bearing age,[87] and pregnancy should be avoided during therapy and for a year after stopping it. High and low doses are required according to the type of psoriasis. Liver function tests and blood counts should be monitored. When used in combination with dithranol,[45] topical corticosteroids,[88] UVB[85] and PUVA,[89,90] there is earlier clearance and longer remission of psoriasis. The side effects are hepatotoxicity, cheilitis, dryness of nasal and buccal mucosae, desquamation of palms and soles, hair loss and arthralgia.

Treatment of Psoriatic Arthritis

This follows the general line of treatment of rheumatoid arthritis and is best supervised by a rheumatologist. Periods of rest and physiotherapy may be needed. Acetylsalicylic acid, paracetamol, phenylbutazone, indomethacin and ketoprofen all have a place in the control of pain and stiffness. Cytotoxic drugs such as azathioprine and methotrexate have been used with some success. Systemic steroids may be occasionally indicated in severe mutilating arthritis.

Treatment of Scalp Psoriasis

Scalp psoriasis is difficult to treat. For mild to moderate cases, a tar spirit lotion such as

liquor picis carb 5% may suffice. Thorough and vigorous daily shampooing is essential for removing scales and medicament. Corticosteroids in gel or lotion formulations are convenient if the scales are not too thick. Intralesional corticosteroids therapy is of value for localised lesions.

Treatment of Nails

There is no effective treatment for psoriasis of nails. In a study by Bedi,[91] seven patients of psoriatic onychodystrophy were treated with monthly injections of triamcinolone acetonide (Kenacort, 0.1 ml of 10 mg/ml) with tuberculin syringe using 22 size needle. Four patients showed complete recovery after 3-4 injections, two showed moderate improvement following 4 injections but relapsed 1-2 months after the last injection. One patient showed no response. Relapse rate was very high. Side effects noted were haemorrhage, pain and reversible atrophy at the injection site.

Systemic methotrexate helps as part of a general effect. Other cytostatic agents are of no value except for a caustic effect obtained with 5-fluorouracil. PUVA treatment may be helpful.

Treatment of Eyelid Psoriasis

In a review article, Wolf[92] stated that psoriasis of eyelids presents a difficult problem and should be treated with low potency steroids (1% hydrocortisone) with rest periods in between. Constant emolliation is extremely effective. The eyelids should never be without a thin film of a moisturizing cream. Tar is an irritant to conjunctiva as is anthralin and are contra-indicated. Some patients benefitted from low dosage retinoid therapy.

Low doses UVB treatment beginning with 0.5 MED and increasing to 2-3 times the original MED given with eye protection is also beneficial.

Other modalities

Dialysis: It has been reported to be an effective therapeutic measure in patients with psoriasis with or without uremia.[93] A circulatory factor (x-factor) is said to be removed from the blood stream.[94] Kumar et al[85] failed to document any significant alterations in the course of psoriasis after haemo-dialysis, as it is presumed that several toxins[94] and hormones[93] are washed out from the subjects undergoing this procedure. Continuous peritoneal dialysis, leukopheresis and plasmapheresis need further evaluation on large series of severe psoriasis patients before these procedures can be recommended as other modalities of therapy.

Hyperthermia: It is an effective mode of therapy,[96] though there is no precise explanation for the effectiveness of this therapy.

Some other new therapeutic modalities are argon laser,[97] carbon dioxide laser,[98] cryotherapy, surgery[99] and intralesional injection of 15(5) — hydroxyeicosatetraenoic acid.[100] Diet supplementation with fish oil[101] may play a useful role in the therapy of psoriasis, a further research in this area is needed.

In the surgical technique, patients of stable plaque psoriasis refractory to medical treatment are taken up. Serial dermatome shaving of the localized area is done under local anaesthesia. Dermabrasion of palmo-plantar pustular psoriasis, and psoriasis over elbows and knees is also tried.

Preventive Measures

The established triggering factors like infection, drugs including practolol, lithium and propranol,[102] trauma to skin, low humidity and emotional stress should be minimised. Psoriasis day care centres are very essential for the care, counselling and education of the patients.

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