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REVIEW

TREATMENT OF THE SO-CALLED INCURABLE SKIN DISEASES

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Most dermatologists must have faced the taunt from their non-dermatologist colleagues that skin diseases are not curable. This may have been true in the past when dermatology was considered to be a leftover speciality, but with the induction of dermatologists who were genuinely interested in the speciality and the consequent progress made during the last few decades, the dermatologists have rightly earned the claim that they can cure/treat a far larger number of diseases compared to any other medical speciality.[1] This review is meant for those who wish to pass on the benefit of the newer developments to their patients. It will not be possible to cover the progress made in all the dermatologic diseases, it is therefore proposed to cover only a few diseases where very significant progress has been made.

Pemphigus

Before the advent of corticosteroids, pemphigus was considered to be almost uniformly fatal.[2-5] With corticosteroids it became possible to control the disease activity in the patients,[2] but most of the patients would develop a relapse when an attempt was made to reduce the dose or on stopping the corticosteroides. Continued administration of corticosteroids over prolonged periods produced their own side effects some of which were as serious and/or fatal.[2,6] Thus although the fatal outcome could be delayed, the situation was far from satisfactory. With the introduction of immunosuppressive drugs, a claim was made that it was possible to manage some of the patients without corticosteroids and in others one could use smaller doses of corticosteroids to control the diseases.[2,3,7] In 1982, we tried a different approach for this disease, employing very high doses of a corticosteroid (dexamethasone) and an immunosuppressive drug (cyclophosphamide), but giving these drugs at fixed intermittent intervals. This treatment schedule called dexamethasone-cyclophosphamide pulse (DCP) therapy has entirely changed the complexion of this disease.[9-13] During the last 12 years or so we have enrolled 330 patients for this treatment, of whom 10 patients have died and 50 have been lost to follow up. Of the remaining 270 patients, 250 patients are in complete clinical remission, 160 of whom have completed the treatment schedule and are being followed up for the possibility of a recurrence. One hundred and ten patients have already been followed up for more than 2 years after stopping the treatment and 20 patients have crossed the 5-year post-treatment follow up period. The cause of death in some of the cases have been unrelated to the disease or its treatment, and the

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patients who are still having active disease are either those who have been inducted tc this treatment only recently or those who have been most irregular in reporting to us. Another major advantage of this treatment schedule is that there are almost no side effects or contra-indications.[14] This treatment can be given to nay patient having diabetes mellitus, hypertension, peptic ulcer, osteoporosis etc, except that diabetic patients need to be administered 8 units of insulin for every transfusion of 500 ml 5% glucose and the routine treatment for any co-existing disease has to be continued. There is as a rule no need to restrict sodium chloride in the diet or give extra potassium, calcium or proteins to these patients because most of them do not develop obesity/weight gain in spite of 100 mg dexamethasone given on 3 consecutive days every 4 weeks (equivalent of 1000 mg prednisolone a day). The major side effects with this treatment schedule consist of increased susceptibility to infections, mainly pyogenic on the skin and candidiasis in the oral mucosa, but this also occurs only during the first phase of treatment when the patient is having ulcers in the skin/ mucous membranes. In some patients there is reactivation of tuberculosis or wide-spread dermatophytosis. These infections need concomitant treatment which may have to be more intensive/ aggressive than usual. The other side effect is the possibility of gonadal failure due to cyclophosphamide. Some females have developed amenorrhoea during this treatment while others have given birth to normal children after having recovered from the disease and completing the treatment. Similarly, azoospermia has also been noticed in some males although we do not have pre-treatment reports of their semen analysis. The sexual function of the individual however, is not effected. When the patient is actually pregnant at the time of reporting for treatment, the DCP should be withheld till the pregnancy is over. Otherwise the patient should be advised to avoid pregnancy till the treatment has been completed.

With the experience gained so far, it seems reasonable to state that pemphigus can now be considered to be a curable disease though it is very essential to administer the treatment as per the appropriate schedule to achieve the optimum results.[13,14]

Collagen vascular diseases

Systemic lupus erythematosus (SLE), progressive systemic sclerosis and dermatomyositis are another group of diseases which are consisdered potentially fatal and by and large incurable. The treatment modalities used for these diseases include corticosteroids,[15] immunosuppressive drugs,[16,17] colchicine,[18] nifedipine,[19] retinoids,[20] cyclosporin,[21] ketanserin,[22] and D-penicillamine of which D-penicillamine[23,24] is the only drug which has been found to slow down the progression of systemic sclerosis, while corticosteroids and some of the immunosuppressive drugs have been found useful for SLE.[15] In 1987, we treated our first case of systemic sclerosis with dexamethasone pulse therapy.[25] This 22-year-old girl had been having tightening of her skin, Raynaud's phenomenon and recurrent ulcers on the finger-tips for the last 8 years, hyperpigmentation of the skin for the last 5 years, and calcification, dyspnoea and dysphagia for the last 3 years. In 4-6 months she started showing

improvement in most of the clinical parameters and in 18 months she had shown almost complete reversal of all her signs and symptoms, except for the dark complexion of her skin. She has now been followed up for 4 years after stopping the treatment and there has been no tendency for recurrence of the disease. Subsequent 11 patients treated with the same treatment schedule have shown similar results except that the degree of reversal of various signs and symptoms varied in different patients. The earlier the treatment is started in this disease, the better the results, and it can now be stated that systemic sclerosis should no longer be called progressive systemic sclerosis (PSS); it can certainly be made static systemic sclerosis (SSS) in almost all the cases and regressive systemic sclerosis (RSS) in most of the cases.

Similarly, we have treated two cases of SLE and 2 cases of dermatomyositis with dexamethasone-cyclophosphamide pulse (DCP) therapy and dexamethasone pulse (DP) therapy respectively and obtained equally satisfactory results.

Vitiligo

The main problem with vitiligo is the social stigma attached to this disease and most people believe that vitiligo is not curable. This belief stems from the treatment failure observed in several patients. PUVA/PUVASOL being the mainstay of treatment for vitiligo[26,27] most patients find it difficult to follow the instructions, either because the PUVA lamps are not available to them, or they find this treatment expensive. In case they opt for PUVASOL, it is difficult to regulate the duration of exposure to sunlight because of the day to day and regional variations in the intensity of sunlight or there may be no sunlight at the time of exposure, or they may be preoccupied with something else at the time when they are expected to expose to sunlight. Obviously the results are not likely to be optimum unless the treatment is taken properly. The second major reason for treatment failure is that quite often if the disease is still active, the patient continues to develop new lesions in other areas even when the old lesions are getting repigmented under the PUVA/PUVASOL treatment.

We believe that the treatment of a disease has to be simple and easy to carry out apart from being safe and effective. For vitiligo therefore, the approach should be, (1) to remove the effect of any of the precipitating factors if applicable to the patient, (2) to control the activity of the disease process if the disease is still active, (3) to stimulate repigmentation in the existing vitiliginous areas, and (4) to resort to the surgical procedures if any of the vitiligo lesions do not respond to the medicinal treatment.

Removal of the precipitating factors :[1] When the lesions are located in the areas coming in contact with the gloves (hands), foot-wear (feet), bindi (centre of forehead), purse (upper part of the breast), spectacle frame (above the external ear), condoms (glans), rubber eraser (lips) or other similar articles made from rubber, elastic or PVC, the patient should be advised to prevent further exposures to these agents. In case the lesions are occurring under the petticoat/ salwar string, the elastic bands of the brassiere or socks or any other item of wearing apparel which causes tight

pressure on the skin, the patient should be asked to loosen the tight pressure or interpose an eight-layer thick cotton cloth (a handkerchief) between the skin and the tight string. The lesions appearing on the knees, elbows, malleoli, knuckles and the front of legs (especially in the athletes, players of outdoor games and children) or those who show Koebner phenomenon depigmentation along a scratch) are caused by trauma and can be helped by wearing padded clothes or cloth bands on these areas to minimize the effect of trauma. Patients having halo nevi are sometimes benefitted if the halo nevus is excised.

Control of the disease activity : Patients who continue to develop new lesions or in whom the old lesions continue to increase in size, need to be given additional treatment to control the activity of the disease because PUVA/PUVASOL alone is not expected to achieve this effect. The two agents that we have found effective for this purpose include, (1) levamisole and (2) corticosteroids. Levamisole[28,29] has been used in a dose of 150 mg orally on two consecutive days (usually Saturdays and Sundays) per week, the dose being reduced to 100 mg for children between 6 and 12 years and 50 mg if the child is less than 6 years. The drug is slow to act and useful only if the disease is slow to spread and limited in extent. Two previous studies[28,29] have shown that the activity of the disease could be arrested in approximately 90% of the patients having active disease. The drug was well tolerated by most of the patients, the main side effects being nausea, vomiting, joint pains and fever seen in some patients only. Systemic corticosteroids are more efective for controlling the disease activity and generally 20 mg prednisolone a day or even on alternate days are sufficient.[1] Most patients however develop obesity and other side effects commonly seen with systemic corticosteroid therapy and these are not acceptable to the patients. We have therefore designed an oral mini-pulse (OMP) regimen[28,30] which consists of giving 10 tablets of betamethasone/dexamethasone (0.5 mg each) as a single oral dose after breakfast on two consecutive days per week. The OMP regimen has been effective in 90% of the cases in controlling the disease activity and is especially recommended if the disease is spreading very fast. The special advantage of the OMP regimen is the significant absence of the side effects. In some cases we have combined OMP regimen with 50 mg cyclophosphamide orally daily throughout the week[28] and in rare instances even dexamethasone pulse therapy in the same way as used for systemic sclerosis has been used.

Repigmentation of the existing lesions : Following control of the activity of the disease and/or removal of the precipitating factor(s), a significant proportion of the patients develop repigmentation of the existing vitiliginous areas without any other concomitant therapy.[29,30] The extent of this spontaneous repigmentation varies in different patients and even in different lesions in the same patient. For those who obtain complete/almost complete repigmentation with this treatment alone, this regimen proves to be very easy and simple, but for those who do not get complete or significant degree of repigmentation, it may become necessary to stimulate repigmentation by other means. This can be done with a variety of agents: The most common method employed for this purpose is PUVA/

PUVASOL. Most dermatologists are familiar with this method but for optimum results it is essential to follow the instructions very carefully.[1] Oral PUVA/PUVASOL is to be preferred for extensive disease, the psoralen is to be administered as a single oral dose (preferably at 10 a m) which should be followed by exposure to UVA/sunlight between 2-4 hours after the oral dose. Mid-day sun (between 12 noon and 2 p m) is best for exposure. The duration of exposure has to be determined by hit and trial for each patient, but it should be able to induce repigmentation in the lesions without producing significant erythema, scaling or vesiculation. Topical PUVA/PUVASOL may be preferred when the disease is limited to a few lesions only, but the incidence of blistering is far higher with topical PUVA/PUVASOL. Most dermatologists therefore prefer diluted psoralens or combine it with topical corticosteroids. Topical corticosteroids alone have also been observed to stimulate repigmentation in the vitiligo lesions[31,32] and the results with topical corticosteroids combined with oral levamisole have been much better compared to oral levamisole alone.[28,29] The major advantage with topical corticosteroids is the simplicity of the procedure compared to PUVA/PUVASOL. The incidence of side effects with topical corticosteroids is far less among the Indians and the side effects are reversible if detected early.[29] Placenta extracts have also been used for the treatment of vitiligo, but the experience so far suggests that this agent is not more effective as compared to the other agents, and the treatment procedure is as complicated as topical PUVA/PUVASOL. On the other hand, the drug is far more costlier and there is an added risk of possible contamination with the HIV virus.

Surgical procedures: Some patients are likely to be left with a few areas which do not respond to the medicinal treatment. Such areas are called residual vitiligo lesions (RVL)[33] and can be left alone if these are not situated on a cosmetically important part of the body. In case however, the patient wants to get rid of even these lesions, they can be subjected to surgical procedures. The surgical procedures used for this purpose include, (1) split thickness grafting,[34] (2) suction blister grafting,[35,36] (3) punch grafting,[33,37,38] and (4) melanocyte grafting.[39] The basic aim of all these procedures is to transplant melanocytes into the vitiliginous area so that these melanocytes can produce pigment and also spread into the adjoining skin to cover up the entire patch(es).

Whatever the procedure adopted, it is of paramount importance that it is reasonably ensured that the disease has been rendered inactive before resorting to grafting because otherwise vitiligo lesions can appear at other areas and even the grafted skin can become depigmented again.

With proper planning therefore, it now seems possible to arrest the activity of the disease in almost every patient, and to induce repigmentation in the vitiligo lesions.

Psoriasis

This is a disease which cannot yet be called curable, but with proper management most patients can be made to lead an almost normal life. Almost any lesion of psoriasis can be made to disappear with topical therapy alone,

using the traditional tar preparations, dithranol or topical corticosteroids with or without salicylic acid.[1] We have however, unnecessarily made ourselves believe that corticosteroids or other ointments cannot be used more than twice a day, and if a lesion does not disappear with two applications a day, we consider the drug to be ineffective. We tend to forget that there are a lot of variations in the quantity of the ointment applied by different individuals on the lesions, and the force with which the ointment is massaged into the skin. The penetrability of the skin in different regions of the body also varies a lot. It is only that proportion of the ointment which reaches the site of the pathology that is going to cause regression of the lesion and unless an adequate amount of the drug reaches the site of action, the lesion is likely to persist. Thus every patient must be trained to use the adequate quantity of the ointment and massage it throughly into the skin as many times a day as is necessary to make the lesion disappear within a reasonable number of days. In case some lesion does not disappear, the ointment may be massaged more thoroughly and a larger number of times to make the lesion disappear. Lesions on the palms and soles or those with lichenification may require even 10-20 applications a day or an occlusive dressing to make them disappear. Next, the patient must be trained not to stop the treatment too soon because otherwise there is a chance for recurrence of the lesions, and even then there is no guarantee that another lesion will not appear at another place for which the same process will have to be repeated. Nevertheless, in most patients two applications a day for a few minutes after the bath in the morning and at night should be enough to keep the patient normal. A patient can be promised a fairly normal life, far better than the diabetics because in psoriasis none of the internal organs runs the risk of damage and psoriatics need not observe any precautions or prohibitions.

A small percentage of psoriatics however, are likely to have more severe forms of psoriasis such as psoriatic erythroderma, pustular psoriasis, psoriasis arthropathy, guttate psoriasis or extensive plaque psoriasis for which topical treatment is either inadequate or inconvenient.[1,40] In most cases these are temporary phases in the routine stable course of plaque psoriasis. Patients in such phases require more intensive and systemic treatment which includes methotrexate, azathioprine, PUVA/PUVASOL, retinoids, cyclosporin or other similar drugs currently under investigation.[40] A significant proportion of patients having guttate psoriasis or even pustular psoriasis respond to one or the other systemic antibiotics or oral ketoconazole given for 2-4 weeks. In each case given systemic drugs it will be necessary to undertake appropriate laboratory investigations to monitor the toxic effects of the respective drugs, if any, and to withdraw the treatment only when the disease has reverted back to the stable phase. Thereafter the patient can be reverted back to the topical treatment alone and managed as described previously.

Acne

Acne should be considered as a phase in the physiologic development of the individual, because it occurs to a

variable extent in almost all the individuals between puberty and the age of 25 years, and coincides with the unstable phase of physiologic (hormonal) changes that occur during the period when a child develops into an adult man or woman.[1] In our opinion, the factors such as poral occlusion with irritant oils/sebum components, and bacterial infection or hypersensitivity are merely precipitating/aggravating factors, because the abnormal sebum and/or bacteria persist even after the age of 25 years whereas the tendency to develop acne decreases remarkably in most of the individuals after that age.

The acne patient has got to be informed that the tendency to develop acne is likely to persist for a variable period till this tendency disappears spontaneously. Throughout this period therefore, it will be necessary to observe certain precautions and take appropriate treatment to adequately prevent the lesions. The necessity to throughly clean the hair with a shampoo, and the face and other acne-prone areas with soap, and avoiding the applications of oil or creams to the hair and face are well known. With these precautions alone, mild cases may stop having acne lesions or experience a significant decrease in its severity. Severe cases however, certainly need more intensive treatment.

Acne can be prevented either by topical treatment or by systemic drugs. A large variety of topical agents are available for the treatment of acne,[1] but whatever the agent selected it has to be applied all over the face and other acne-prone areas because otherwise acne lesions can appear on the areas where the topical agent is not applied. We therefore consider it necessary to design and use the agent more like a cosmetic rather than a drug. Since bacteria have a significant role to play in the pathogenesis of acne and lactic acid/lactate is a strong broad-spectrum antibacterial agent[41] produced by the skin itself, we prefer to use 5% lactic acid in a suitable base for this purpose and find it fairly effective in preventing acne lesions.[42] Its use however has to be continued even when there are no lesions. Thus the slogan, "When stepping into the acne age, start using lactic acid/lactate, and save your face". Although other topical agents can also be used in a similar manner,[1,43,44] topical antibiotics have the risk of causing contact hypersensitivity and/or bacterial resistance, retinoic acid can lead to irritation, sulphur preparations have the disadvantage of bad smell, while calamine base preparations cannot be used during the day for cosmetic reasons.

Systemic drugs useful for acne include a wide range of antibiotics/antibacterial agents including ketoconazole[42] and these are generally more effective and easy to use. But since tendency to develop acne can last several years, it would be unwise to continue to take oral antibiotics for all that period. The practice of using sub-therapeutic doses of antibiotics is even more hazardous because this can lead to bacterial resistance and make the drug useless even for other infections. The best compromise therefore is to use systemic drugs only for those periods when topical treatment alone is not sufficient to provide adequate control of acne.[1] Systemic therapy thus may be limited to only 4-8 week periods at a time and repeated whenever necessary.

Further, several dermatologists advise their patients to avoid oily foods, not realising that the sebaceous gland is a secretory gland and not an excretory gland, and it can manufacture all the oily components of the sebum irrespective of their levels in the blood. We feel it is unnecessary to burden the patient with unconfirmed dietary prohibitions.

There are several other diseases which can also be managed much better with a similar rational approach. Most of the patients who do not recover from their disease are those who are not properly committed to complete the treatment. Treating a disease is like fighting a war and if the war has to be won, it is essential to accurately assess the enemy power (extent and severity of the disease), to employ forces (drugs) adequate to out-do the enemy power, to evaluate the results (recovery), and to induct more forces (augment the treatment) if the desired result has not been achieved as per the time plan. To prevent relapses it is equally important not to be in a hurry to withdraw the treatment. It is better to err for a longer treatment rather than stop it too early.

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