PHOTOCHEMOTHERAPY OF VITILIGO WITH ORAL TRIOXSALEN AND TROPICAL SUNLIGHT

JONATHAN H. ADDY
Department of Medicine & Therapeutics
University of Ghana Medical School
P.O. Box 4236, Accra, Ghana

SUMMARY

Six black adults suffering from widespread symmetrical vitiligo (5 with and 1 without associated autoimmune disease) of 2 to 10 years duration were treated for 18 months on alternate days with orally administered trioxsalen, 10mg, followed 2 hours later by 30 minutes lesion-exposure to tropical midday sunlight. Whereas all lesions became intensely but transiently pruritic and erythematous immediately after each treatment session, repigmentation started in 4 weeks (i.e. after several treatment sessions) from normal skin at periphery of lesions and around hair follicles within lesions as pin-head-sized black macules which enlarged slowly and eventually coalesced to obliterate the white patches. Lesions overlying soft tissue and muscle bulk pigmented well while those over bony prominences failed to pigment satisfactorily. Re-pigmented areas have remained stable and cosmetically acceptable for up to 5 years. Two patients complained of burning sensation after each treatment but were able to complete the treatment. Response to above treatment with over 75% (in 4 patients) and 50% (in 2 patients) repigmentation of originally diseased skin without significant side effects led to the conclusion that photochemotherapy utilizing trioxsalen and sunlight was effective against widespread vitiligo in dark-skinned patients in the tropics.

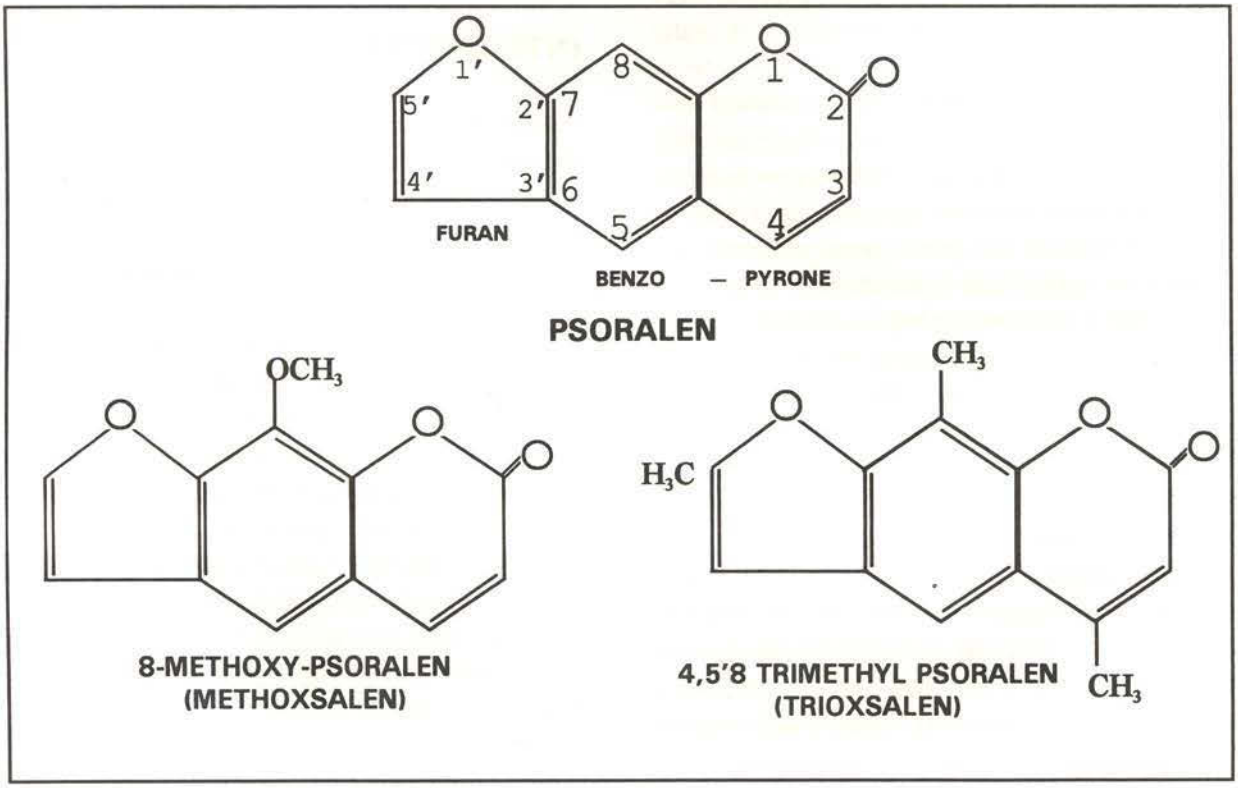
INTRODUCTION

Vitiligo is an acquired idiopathic macular loss of pigmentation of otherwise normal skin devoid of all other epidermal changes except destruction of melanocytes. It presents clinically as round or oval white patches measuring a few millimetres to several centimetres in diameter. Lesion margins are usually clear-cut abutting directly on normally pigmented skin or separated from same by a ring of intermediate colour producing a three colour pattern variety known as trichome vitiligo.[1] Although vitiligo is seen frequently in normal people, the disease seems to occur at greater frequency in patients with thyroid disease, Addison's disease, pernicious anaemia, alopecia areata, adult onset diabetes mellitus and in those with positive family history of vitiligo.[2,3] In fair-skinned individuals living in temperate and cold climates with little sunshine for most of the year vitiliginous skin is hardly discernible from

normal skin in winter, disfigurement is therefore minimal, and indeed the disease can sometimes be left untreated. However in black- and brown-skinned people living in the tropics, it is a distressingly disfiguring condition especially when it involved the face and other exposed parts. The contrast between normal and diseased skin is so sharp and conspicuous that the sufferer is unable to function with confidence in society, treatment is therefore imperative. Psoralens in combination with ultraviolet-A (PUVA) therapy rediscovered and introduced into orthodox medicine by Egyptian dermatologists[4] and subsequently improved and widely publicised by North American and European medical scientists and dermatologists [5,6,7] is to date the best known treatment for vitiligo. Other forms of treatment such as topical corticosteroids[8] and topical fluorouracil[9] have achieved only very limited success in the hands of a few workers. The recently introduced combination of phenylalanine and ultraviolet-A[10,11] sounds promising but has not been fully tested.

Psoralens are naturally occurring substances which belong to a family of compounds known as furocoumarins which are heterocyclic aromatic compounds built by the fusion of a benzene nucleus to a pyrone ring to form a coumarin or benzopyrone, fusion of which to a furan ring produces the basic furocoumarin structure. See Fig. 1. Psoralens for medicinal use were originally extracted from plants such as *Ammi majus*. Three classes namely: 8-methoxy, 5-methoxy and 4,5'8 methyl compounds have been synthesized in the laboratory and all have been found to be highly photo-sensitizing like the original plant extracts, and suitable for photochemotherapy as well. Detailed comparative studies[12] have identified the 8-methoxy compounds to be the most photosensitising and also most efficient in producing pig-

Figure 1. Structure of Psoralen, Methoxsalen and Trioxsalen



mentation as well as yielding unwanted side effects even when the dose of UVA was carefully controlled by use of measured artificial light. Since the 4,5'8 methyl compounds are known to be the least photosensitizing amongst the psoralens[13,14,15] trioxsalen was chosen for this trial for which no controlled artificial sources of UVA was available, and therefore sunlight itself had to be employed.

Most authors have adopted a working classification of vitiligo based on number and distribution of lesions.[16,17] Thus where lesions are few the disease has been labelled as focal, segmental or dermatomal (confined unilaterally to one or more adjacent dermatomes). Where lesions are many it has been labelled as generalised, which may be scattered, usually bilaterally symmetrically, or limited to the extremities and around orifices. The purpose of this paper is to report the effect of modified PUVA therapy which entailed systemic (orally administered) trioxsalen (4,5'8-trimethylpsoralen) followed by exposure to sunlight on vitiligo of the generalised/scattered bilaterally symmetrical type.

CLINICAL MATERIAL AND METHODS

Six adult black Ghanaians suffering from generalised and symmetrically disposed vitiligo involving over 50% of total skin area were the subjects of this therapeutic study. After explaining the modalities of the treatment and emphasising the necessity of exposure to sunlight 2 hours after swallowing a prescribed dose of trioxsalen, their consent was obtained. They were then admitted to hospital for clinical investigation aimed at identifying associated conditions, establishing fitness to undertake the treatment, and starting the regime under controlled hospital conditions. This initial close supervision was to ensure compliance over the projected long term period of self supervision which was essential for success. Liver disease was excluded by clinical examination and routine liver function tests. Haematological tests were done to establish baseline profiles. Physical examination, fasting blood sugar, urine sugar, thyroid function tests, blood urea and electrolytes, and serum cortisol levels were done in order to detect possible co-existence of autoimmune and endocrine diseases — where these were detected appropriate therapy was instituted in addition to the treatment for the vitiligo.

PHOTO-CHEMOTHERAPEUTIC METHOD

Psoralen ultra-violet-A (PUVA) was modified to suit local conditions by substituting natural sunlight for artificial ultra-violet-A (UVA) which was not available in the hospital. Ten (10) milligram of trioxsalen was swallowed on alternate days at mid-morning following a light breakfast. Two hours after the ingestion of the trioxsalen, the white vitiliginous patches were exposed to sunlight for 30 minutes by placing the patient in an unshaded open space (wearing protective dark glasses) from about 12 noon to 12.30 p.m. Treatment was instituted on alternate days, i.e. 3 times a week for 2 weeks, after which the patient was discharged with instructions to continue same at home. Treatment was not attempted on rainy or cloudy days. Patients were seen at 6 weeks intervals for review. Total duration of treatment was 18 months. Clinical photographs were taken before the onset of treatment and at the end of 18 months of treatment.

RESULTS

Six patients (4 males and 2 females) aged 38 to 65, mean 49 8±10 were treated for the full 18 months. Table 1 is a summary of the clinical features of the 6 patients. Duration of the illness before onset of treatment ranged from 5 to 20 years, mean duration being 11.7±5.3 years. Percentage of skin involvement computed by using the rule of nines ranged

from 50% to 80% (mean 65.8±14.3). Trunk and limbs were involved in 6 patients but head and neck were spared in 2 patients (1 man and 1 woman) and genitalia were spared in 3 other patients (1 woman and 2 men). In only one patient was an associated auto-immune disease not detected; 2 patients both male had non-insulin-dependent diabetes which required treatment with oral hypoglycaemic agents, one had alopecia areata and two females had thyroid disease — the younger woman aged 40 had frank thyrotoxicosis and the older woman (48) had a goitre with evidence of myxoedema. Apart from the above

Table 1. Summary of Clinical Features and Response to Treatment

Case	Age	Sex	Duration Years	Associated Disease	% Skin Involvement	Head & Neck	Trunk	Limbs	Genitalia	Response to Chemotherapy
1	56	M	10	NIDDM*	80	+	+	+	+	Excellent***
2	40	F	5	Thyrotoxicosis	75	+	+	+	–	Good**
3	65	M	20	Nil	80	+	+	+	–	Excellent
4	48	F	15	Goitre & Myxoedema	50	–	+	+	+	Good
5	38	M	8	Alopecia Areata	60	+	+	+	+	Excellent
6	52	M	12	NIDDM*	50	–	+	+	–	Excellent

*NIDDM = Non-insulin Dependent Diabetes Mellitus **Good >50% repigmentation *** Excellent >75% repigmentation

Figure 2. Extensive Vitiligo before Treatment

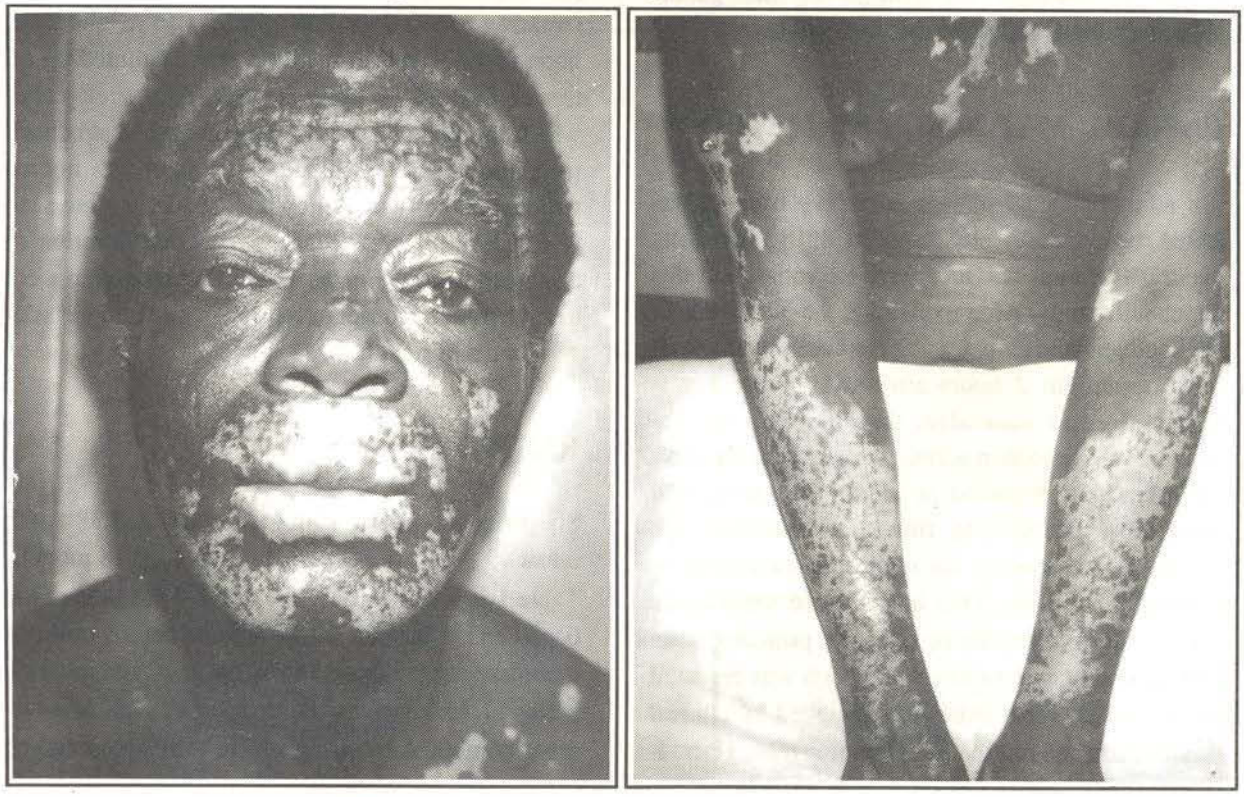
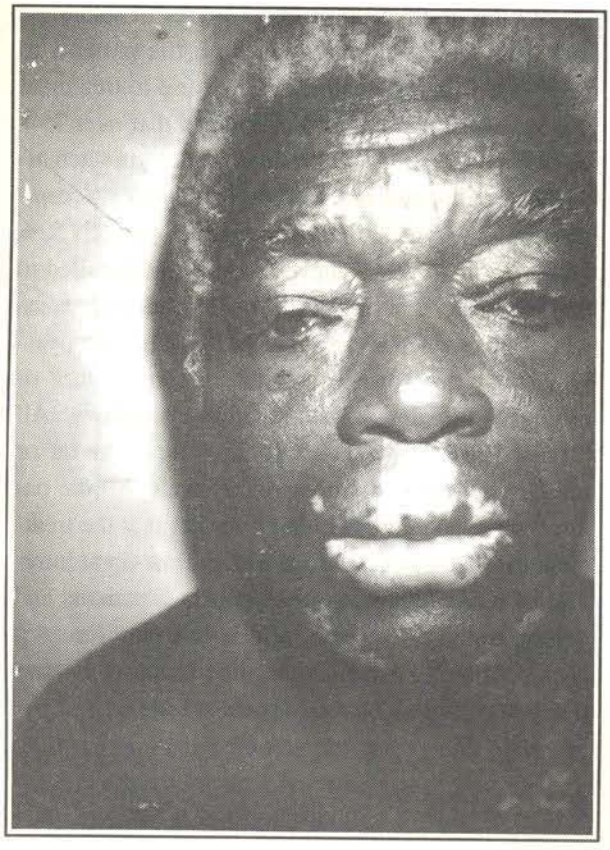
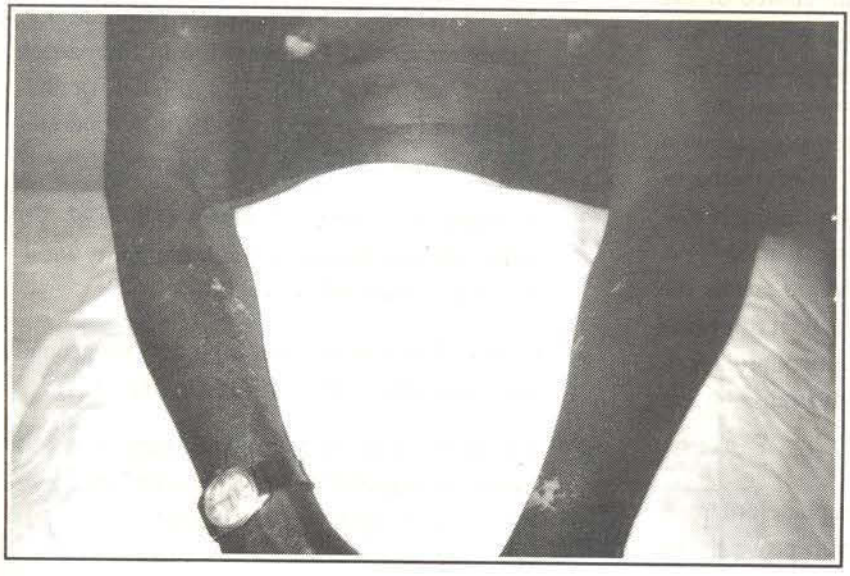


Figure 3. **Same Patient as in Figure 2 after Eighteen Months Treatment with Photochemotherapy as Described in the Paper.**





associated conditions which were not contraindications for the photochemotherapy, the blood profile, liver function tests, urea, electrolytes and cortisol levels before and after treatment were normal in all the 6 patients.

All six patients repigmented. Response to photochemotherapy was considered excellent in 4 in whom over 75% of the original white areas repigmented — See Figs. 2 and 3. In the remaining 2, repigmentation occurred in approximately 50% of the original white areas. Diseased (white) areas overlying muscle bulk and soft tissue repigmented well while those overlying thin soft tissue and bony prominences pigmented in patches or not at all. Side effects were minimal. Erythema of vitiliginous skin associated with severe burning sensation occurred in 2 patients. In none were the side effects severe enough to warrant termination of treatment.

DISCUSSION

The true incidence of vitiligo in Ghana is unknown. The disease is known to occur in all races and the general incidence amongst Caucasians was estimated at 1% with a wide variation of 0.14% to 8.8% in various population groups.[16,17] There is no reason or clinical impression to warrant belief that the incidence is greater in the black races. George[18] found an incidence of 6% in patients attending a hospital dermatology clinic in Ibadan, Nigeria. The disease is more conspicuous and demand for treatment is apt to be more urgent in black patients. It is interesting to note that the vitiligo in 5 out of the 6 patients treated in this work was associ-

ated with an auto-immune disease, a phenomenon noted earlier by Grimes *et al*[19] (1983) who concluded that vitiligo in black patients is an auto-immune disease. The six chosen for this pilot therapeutic study do not represent the range of affected age groups in Ghana — they were selected because they demanded treatment most vehemently and could afford to buy the drugs from abroad. Whereas white patients can ignore the white patches of vitiligo especially in the winter months and get away with minimum embarrassment, black patients cannot — they have no options at all in that cosmetic camouflage with commercial make-ups pigments was unsatisfactory and total bleaching an acceptable option with whites, was frowned upon by black Ghanaians, most of whom were prepared to undergo treatment aimed at repigmentation even after being told that photochemotherapy was a cumbersome procedure.

The disadvantage of sunlight was that it contained sunburn wavelengths, i.e. ultra-violet-B. In order to avoid sunburn in the white patches therefore, exposure time was kept to 30 minutes found by preliminary studies to be the minimum effective exposure time. The potential danger of sunburn in the white patches was further avoided by the choice of the synthetic 4,5'8 methyl psoralen which was known to be capable of stimulating melanocytes without preliminary phototoxic reaction[11] as against the 8-methoxy psoralens which stimulated pigmentation invariably via preliminary phototoxic erythema or even blistering.[9] Trioxsalen is therefore strongly recommended where there are neither artificial UVA sources, nor adequate instrumentation to enable the delivery of precise doses of radiation, be it from sunlight or artificial sources. The necessity of prolonged treatment (18 months for this study) must be explained to the patient at the outset.

Furthermore a good clinical photograph before treatment is started is essential in order to prove to the patient at an early stage that the treatment is effective. In all the 6 patients reported here, islands of pin-head-sized perifollicular pigmentation were clearly discernible after only 4 weeks of treatment and their visualization encouraged the patients to persevere with the treatment. Response to treatment was excellent in 4 out of 6 patients in that over 75% of original diseased skin became well pigmented after 18 months and has stayed cosmetically acceptable for 1 to 5 years. In the remaining 2 patients 50% repigmentation was achieved. Areas which failed to pigment were skin of back of hands and other areas where subcutaneous tissue was thin or in skin overlying bony prominences; — the reason for lack of response to treatment in these areas is unknown. All diseased skin overlying soft tissue such as fat or thick muscle bulk pigmented very well. All the patients were unanimous in their verdict that the treatment had been worth their while. Follow-up at intervals of 6 months for up to 5 years in 2 patients had demonstrated no relapse, and it has therefore not been possible to establish the time frame of relapse if any nor a policy on retreatment schedules.

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