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LETTERS TO THE EDITOR

Systemic Immunotherapy with Topical Dinitrochlorobenzene as Additional Treatment of Alopecia Areata

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Sir,

Topical immunotherapy is the most effective modality in the treatment of severe alopecia areata (AA) (1). However, whether topical sensitizers act only locally and/or also systemically is not well documented. The mechanism of action of topical sensitizers appears to have an immunologic basis. Happle et al. suggested an influence on local immunoregulation, noting denser peribulbar round cell infiltrates at sites treated with topical dinitrochlorobenzene (DNCB) (2), and a decrease in the peribulbar CD4/CD8 lymphocyte ratio after treatment with topical sensitizers (3). In contrast, certain phenomena cannot be explained by an effect on local immunoregulation, as hair regrowth can occur at sites distant from the application (4).

We have studied topical DNCB therapy as systemic immunotherapy, based on its likely stimulation of T-helper 1 (Th1) responses (5, 6), and our recent reports of its efficacy in treating chronic prurigo (7) and atopic dermatitis (8). In the present study, we examined topical DNCB therapy on the extremities as additional treatment in patients with severe forms of alopecia and observed an excellent response rate of 65% after 20 weeks of therapy.

MATERIAL AND METHODS

Patients with AA recruited for this study had extensive AA defined as >40% loss of scalp hair, multiple AA defined as more than 10 patches of hair loss, or alopecia totalis (AT). Four males and 16 females, with an age range of 12–64 years (mean 31.9 years), were included in the study (Table I). The mean duration of AA was 13.7 months (range 3–60 months). Fifteen patients had extensive AA, 3 had multiple AA, and 2 alopecia totalis (AT) (Table I). One patient (patient 19) had severe atopic dermatitis, and one (patient 11) had mild atopic dermatitis. None had other autoimmune diseases.

The patients were initially treated with cryotherapy and/or topical corticosteroids for more than 12 weeks without any response prior to inclusion. DNCB treatment was then added to the ongoing therapies. The efficacy of DNCB therapy was evaluated at the end of 20 weeks. Written informed consent was obtained.

The patients first received an application of 2% DNCB/acetone solution (2% DNCB) to a 1-cm^2 area on their upper arm to exclude prior sensitization. Sensitization was then achieved with 1 or 2 applications of 5% DNCB on the arm, followed by weekly applications of DNCB (0.5–0.02%) on a 2.5 cm^2 area of the upper arm or thigh, intermittently. If a strong cutaneous reaction occurred, the concentration of DNCB was reduced.

Statistical significance was determined using the Mann–Whitney U-test. The level of significance was $p < 0.05$.

RESULTS

An excellent response (>75% hair regrowth) was observed in 65% (13/20) of the patients at the end of 20 weeks of DNCB therapy (Table I). The mean onset of stop of hair loss was 3.3 weeks (range 2–8 weeks), and the mean onset of hair regrowth was 4.5 weeks (range 2–8 weeks). Two patients showed a partial response. However, 5 of the 20 patients showed no response.

We investigated factors associated with the prognosis of DNCB therapy (Table II). The mean age of onset of AA was significantly higher in successfully treated patients than in unsuccessfully treated patients. Thus, patients with a later onset of AA appear to respond better to additional DNCB therapy.

Laboratory parameters did not show any abnormalities (data not shown).

DISCUSSION

We obtained more than 75% hair regrowth at the end of 20 weeks of DNCB therapy among 65% of our patients. The efficacy obtained in this study does not differ from that obtained using traditional methods of local immunotherapy (9). The mean onset of hair regrowth (4.5 weeks) in this study was similar to that induced by traditional methods (6 weeks) with another sensitizer, squaric acid dibutylester as reported by Chua et al. (10).

Our results support the finding that topical DNCB therapy acts systemically with an efficacy as high as traditional methods. In addition, we confirmed early stopping of hair loss at 3.3 weeks after starting DNCB therapy. This phenomenon is thought to be one advantage of DNCB therapy as systemic treatment.

We cannot rule out the possibility that the effect from systemic DNCB treatment is synergistic to local therapy. In this study, the mean age at onset was the only factor that influenced the prognosis (Table II), which is consistent with a previous report using topical immunotherapy with diphencyprone (11). It has been reported that

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Table I. Results of systemic immunotherapy with dinitrochlorobenzene in patients with alopecia areata

Patient number	Age/Sex	Type of alopecia	Duration of alopecia (months)	Loss of scalp hair (%)	Onset of stop of hair loss (weeks)	Onset of hair regrowth (weeks)	Hair regrowth at 20 weeks (%)
1	40/F	AT	12	100	–	2	100
2	18/M	AT	4	100	–	8	100
3	45/F	AA	3	60	2	5	100
4	55/F	AA	4	50	2	3	100
5	30/F	AA	36	50	3	4	100
6	36/F	AA	4	70	3	4	> 75
7	52/F	AA	5	60	2	3	> 75
8	64/F	AA	5	70	4	6	> 75
9	23/M	AA	12	70	3	3	> 75
10	60/F	AA	4	40	3	4	> 75
11	20/F	AA (multiple)	3	30	8	8	> 75
12	20/F	AA (multiple)	18	40	2	3	> 75
13	25/M	AA (multiple)	24	60	4	4	> 75
14	12/F	AA	12	50	4	4	25–50
15	43/F	AA	60	70	–	6	< 25
16	15/M	AA	3	40	–	–	0
17	16/F	AA	48	60	–	–	0
18	22/F	AA	4	80	–	–	0
19	18/F	AA	4	60	–	–	0
20	24/F	AA	8	50	–	–	0

AT: alopecia totalis; AA: alopecia areata affecting more than 40% of the scalp; AA multiple: Ten patches or more of alopecia areata.

Table II. Comparison between successfully (> 75% hair regrowth at 20 weeks) and unsuccessfully treated patients (mean $\pm SD$)

	Successfully	Unsuccessfully
Mean age at onset of alopecia (years)	36.7 ± 16.8	19.7 ± 8.9*
Mean duration of alopecia (months)	10.3 ± 10.1	19.9 ± 23.8
Mean loss of scalp hair (%)	61.5 ± 21.2	58.6 ± 13.5
Mean concentration of weekly DNCB (%)	0.15 ± 0.08	0.26 ± 0.17

*$p = 0.0214$.
DNCB: dinitrochlorobenzene.

the duration of AA also influences the prognosis (9, 11), although we did not find such a correlation in our study.

The DNCB treatment was well accepted by our patients. The simplicity of application requires only a 2.5 cm^2 area on the upper arm and thigh, intermittently, and is not time-consuming or painful. Swelling of regional lymph nodes was not seen.

The possibility that topical sensitizers act systemically was suggested by studies treating AA (4, 12). Salvo et al. (13) reported the efficacy of systemic immunotherapy with cutaneous DNCB in papillomavirus infection of the cervix uteri. Dearman & Kimber (5) proposed that topical DNCB will stimulate Th1 responses in mice. Stricker et al. (14) clinically tried topical DNCB therapy for HIV infection, where the Th1 response is deficient. We have attempted topical DNCB as a systemic immunotherapy for several diseases in dermatology, and we recently reported its efficacy in treating chronic prurigo (7) and atopic dermatitis (8), where Th2 cells might play a pathogenic role. Teraki et al. (15) reported that patients with localized AA show a predominance of Th2 responses. Therefore, the distant effects of DNCB in the present study may be related to a systemic stimulation of Th1 responses induced by repeated application of topical DNCB.

Although our data support the hypothesis of a systemic effect of topical DNCB in the treatment of alopecia, this efficacy might be synergistic with concurrent local therapies. Thus our results should be interpreted with caution, as is the case for most open studies.

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Two Unusual Cases of Kaposi's Varicelliform Eruption

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Sir,

Kaposi's varicelliform eruption (KVE) is characterized by the sudden appearance of numerous vesicles or erosions in a patient suffering from any other skin disease. The most common causative agent is herpes simplex virus (HSV) and by far the most common underlying dermatosis is atopic dermatitis (1). We report two patients who had KVE on a background of psoriasis and lupus vulgaris, respectively, which to our knowledge has not been reported so far.

CASE REPORTS

Patient 1

A 52-year-old bus driver with previous attacks of psoriatic erythroderma presented with the sudden appearance of multiple vesicular lesions predominantly over the right side of the face. The patient had been taking methotrexate at 20 mg per week for the past 6 weeks. There was no prior history of herpes labialis or gingivostomatitis and there were no systemic symptoms. The lesions were 5–10 mm eroded papulovesicles situated over the scalp, forehead, eyebrows, nose and lips. A few isolated lesions were present on the chest and upper abdomen. A Tzanck smear taken from the lesions demonstrated numerous multinucleated giant cells. The pretreatment HSV antibody titer in the patient's serum was 40 (starting dilution for testing 1:10). HSV-1 infection was confirmed by antigen detection using indirect immunofluorescence (IIF) in smears as well as isolates from the scrapings and vesicular fluid processed *in vitro* cell line.

Hemogram, liver and renal function tests were within normal limits and the patient was HIV negative. A diagnosis of KVE was made because of confirmation of HSV-1. Methotrexate was stopped and the patient was given acyclovir, orally, 400 mg 3 times a day. Complete subsidence of lesions was seen after 7 days of therapy, and the HSV antibody titer fell 4-fold. The patient's psoriasis continued to improve during this period and he was restarted on methotrexate at 15 mg per week, after subsidence of the vesicular lesions. Since then, he has had no relapse of the herpes lesions.

Patient 2

A 30-year-old office attendant, known to have lupus vulgaris of the perineum and right buttock, was started on 4-drug anti-tuberculous therapy. Two weeks later, he suddenly developed multiple painful erosions along the anal verge, which rapidly spread over 24 h to involve the edge of the lupus vulgaris lesion in the form of large serpiginous erosions with polycyclic borders. There was no prior history of oral or genital herpes and the patient was heterosexual. ELISA for HIV was negative. A Tzanck smear from the erosions revealed numerous multinucleate giant cells with intranuclear inclusion bodies. Eczema herpticum was diagnosed and he was