Treatment of severe atopic dermatitis by topical immune modulation using dinitrochlorobenzene

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We present the results of a small uncontrolled pilot trial which suggest that contact sensitization to dinitrochlorobenzene and repeated weekly applications significantly improve the clinical status of severe atopic dermatitis in adults. Although no changes were noted in circulating levels of either lymphocyte subset populations or the serum cytokines assayed in this trial, our observations may be due to topical immune modulation by dinitrochlorobenzene. Larger controlled studies of dinitrochlorobenzene treatment in atopic dermatitis are warranted. (J Am Acad Dermatol 2000;42:687-9.)

Atopic dermatitis is a common skin disorder that is increasing in prevalence. Although several therapies are used in an attempt to control the chronic cutaneous inflammation seen in this disease, no treatment available to date has sufficient efficacy and tolerability for successful long-term use in most patients. Because atopic dermatitis is associated with several immunoregulatory abnormalities, current pathogenetic theories emphasize an immunologic basis for this chronic dermatosis. Many authorities regard this as a disorder in which there is a predominance of helper T-cell type 2 (T_H2) immune responses relative to T_H1; a recent article postulated sequential activation of T_H2, then T_H1 cells.[1] Alternative treatment modalities would be useful in patients responding inadequately to currently available treatments. We therefore investigated the possibility that atopic dermatitis might respond to a topical immune modulating agent such as 1-chloro-2,4-dinitrobenzene (DNCB).

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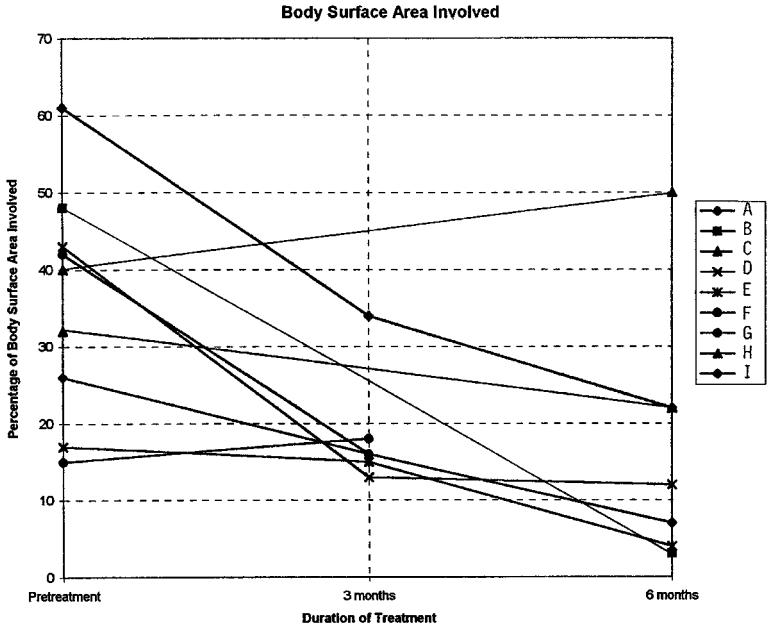

Fig 1. Percentage of body surface area involved for 9 patients enrolled in the trial at pretreatment and after 3 months and 6 months of treatment with weekly applications of DNCB patches.

DNCB has been used extensively as an experimental contact sensitizer and in the treatment of several skin disorders, including warts and alopecia areata. More recently, DNCB has been used in the treatment of HIV infection as a topical immune modulator.[2,3] It has been proposed that DNCB acts by upregulating T_H1-type immune responses in patients infected with HIV. This suggested to us that DNCB might be of use in the treatment of atopic dermatitis.

We therefore undertook a pilot study to investigate the possibility that weekly applications of DNCB might be beneficial in the management of chronic, severe atopic dermatitis recalcitrant to treatment with conventional therapies. A total of 9 adult patients with atopic eczema were enrolled in a 6-month uncontrolled observational trial. Baseline and serial clinical evaluations were made by several dermatologists experienced in the management of this disorder. In addition, several immunologic parameters were monitored during the period of observation.

METHODS

The study patients included men and women older than 18 years with long-standing atopic dermatitis and no known prior exposure to DNCB. After informed consent had been obtained, baseline clinical assessment and immunologic profiling were performed as described later. An occlusive patch containing 1.5 mg of crystalline DNCB was then applied to an unexposed area, such as the buttock, thigh, or upper arm for 12 to 18 hours. Successful sensitization was achieved when the treated site showed erythema, edema, vesiculation, and/or frank eczematous changes. One month later, the study subjects began weekly 12- to 18-hour applications of patches containing from 50 to 500 μg of DNCB. The amount of DNCB used in the weekly treatment patches was determined by the clinicians conducting the trial and was the amount estimated to elicit a reaction of mild erythema and edema, with slight, if any, vesiculation at 24 to 72 hours after patch application. These lesions regularly healed within a week.

Clinical assessment involved an evaluation of the extent and severity of atopic dermatitis with the standard criteria developed by Hanifin and Rajka.[4] A baseline assessment was performed before sensitization with DNCB and then serially during the 6-month treatment period. Scoring was based on the extent of body surface area affected. Immunologic profiling was performed by obtaining peripheral blood mononuclear cells and analyzing by flow cytometry for total $CD3^+$, $CD4^+$, $CD8^+$, and $CD19^+$ lymphocytes subsets as well as natural killer (NK) cells. In addition, serum concentrations of cytokines interleukin 2 (IL-2), IL-4, IL-5, and interferon gamma were determined by enzyme-linked immunosorbent assay.

RESULTS

Weekly application of low doses of DNCB (50-500 μg) did not aggravate the disease and led to a signif-

icant decrease in the total body surface area of involved skin in this small cohort of patients with severe atopic dermatitis (Fig 1). At baseline clinical assessment, the patients had an average total body surface area involvement of 36%, which decreased to 19% and 17% after 3 months and 6 months of weekly applications of DNCB, respectively. Seven of the 9 patients had a decrease in total area of involvement. The dermatologists monitoring these patients also thought that there was an overall decrease in the severity of involvement, including the two patients who did not show a decrease in surface area of involvement. The only adverse clinical event noted during the pilot trial period was the diagnosis of an intermediate grade B-cell lymphoma in one patient during the study period, which the treating oncologist did not think was related to the DNCB administration. That patient's eczema had been reduced significantly with DNCB administration and then worsened when the applications were terminated.

No significant changes in any of the lymphocyte subsets or NK cells were noted. These results are similar to findings in a trial involving normal subjects who underwent an identical DNCB treatment protocol (L. B. Mills, unpublished observations). Serum concentrations of the cytokines assayed were also unaffected in the patients with atopic dermatitis by the DNCB applications. These results are similar to the unpublished observations already noted involving normal subjects undergoing weekly applications of DNCB.

DISCUSSION

Although this is a small uncontrolled pilot trial, the trend toward significant clinical improvement with use of DNCB was evident. Patients noted reduction of their dermatitis and spontaneously reported decreases in the amounts of topical steroid preparations applied and oral antihistamines consumed to control their disease. Although none of the immunologic parameters monitored showed any obvious changes, studies of local tissue perturbations in lymphocyte subsets and cytokines may be more relevant in attempting to unravel the mode of action of this immune modulator. Our observations suggest that larger, controlled studies of DNCB treatment in atopic dermatitis are warranted. It appears that DNCB sensitization and treatment may act as an adjunct to decrease the patient's need for anti-inflammatory drugs over a long-term program of therapy.

In view of the new systemic[5,6] and topical treatments[7,8] proposed for atopic dermatitis, it seems appropriate to consider the potential risks and benefits of these various therapies. Both interferon gamma and tacrolimus are expensive, and interferon gamma therapy is not cost-effective at this time; tacrolimus, however, will find use in most developed countries. DNCB, on the other hand, is inexpensive and can be used worldwide where applicable. The gravamen that this chemical is a mutagen in vitro has been negated by several clinical studies in humans and animals.[9]

Even more interesting is why tacrolimus and DNCB, which appear to have opposite immunologic effects, might produce approximately equal responses in atopic dermatitis. Tacrolimus prevents contact dermatitis,[10] but the comparison may be more illusory than real. More study is required.

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REFERENCES

1. Grewe M, Bruijnzeel-Koomen CAFM, Schopf E, Thepen T, Langeveld-Wildschut AG, Ruzick T, et al. A role for Th1 and Th2 cells in the immunopathogenesis of atopic dermatitis. Immunol Today 1998;19:359-61.
2. Mills LB. Stimulation of T-cellular immunity by cutaneous application of dinitrochlorobenzene. J Am Acad Dermatol 1986;14: 1089-90.
3. Stricker RB, Goldberg B, Epstein WL. Topical immune modulation (TIM): a novel approach to the immunotherapy of systemic disease. Immunol Lett 1997;59:145-50.
4. Hanifin J, Rajka G. Proceedings of First International Conference on Atopic Dermatitis. Acta Derm Venereol Suppl (Stockh) 1980;92:44-7.
5. Hanifin JM, Schneider LC, Leung DYM, Ellis CN, Jaffe HS, Izu AE, et al. Recombinant interferon gamma therapy for atopic dermatitis. J Am Acad Dermatol 1993;28:189-97.
6. Reinhold U, Kukel S, Brzoska J, Kreysel HW. Systemic interferon gamma treatment in severe atopic dermatitis. J Am Acad Dermatol 1993;29:58-63.
7. Ruzicka T, Bieber T, Schopf E, Rubins A, Dobozy A, Bos JD, et al. A short-term trial of tacrolimus ointment for atopic dermatitis: European Tacrolimus Multicenter Atopic Dermatitis Study Group. N Engl J Med 1997;337:816-21.
8. Boguniewicz M, Fielder VC, Raimer S, Lawrence ID, Leung DYM, Hanafin JM. A randomized vehicle-controlled trial of tacrolimus ointment for treatment of atopic dermatitis in children. J Allergy Clin Immunol 1998;102:635-42.
9. Stricker RB, Goldberg B. Safety of topical Dinitrochlorobenzene. Lancet 1995;346:1293.
10. Lauerma AI, Maibach HI, Granlund H, Erkko P, Kartamaa M, Stubb S. Inhibition of contact allergy reactions by topical FK506 [letter]. Lancet 1992;340:8818.